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Original Communications

THE SIGNIFICANCE OF RHEUMATIC ACTIVITY IN CHRONIC RHEUMATIC HEART DISEASE*

PART I. INTENSITY AND EXTENT

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DURING the past few years further study of rheumatic heart disease has resulted in more comprehensive knowledge of the clinical and pathological facts concerning it. The occurrence of cardiac injury incident to acute rheumatic polyarthritides, chorea, and tonsillitis is well known,¹⁻¹⁴ and efforts are now made early to prevent damage to the heart.^{2, 8, 12, 13, 15-30}

There exist, nevertheless, many adult patients who are incapacitated from rheumatic cardiac disease. How to manage them is still relatively poorly understood. They offer a complex therapeutic and social problem for which a satisfactory solution has not yet been found.

Recent observers have regarded the late stages of rheumatic cardiac disease as the end-result of an infection long since subsided.³¹⁻³⁵ Studies of rheumatic lesions^{2, 11, 14, 24, 36-50} substantiate the importance of the continuance of the active inflammatory process. Impairment of cardiac function cannot always be attributed, therefore, solely to mechanical strain on the myocardium from stenosed and insufficient valves.

The marked disability of older patients and many of the symptoms and signs exhibited by them resemble similar phenomena presented by

*This article is the second of a series to be published on investigations at the New York Cardiac Shop, which was a special project of the Committee on Cardiac Clinics of the New York Heart Association. This work was made possible by grants from the Hofheimer Foundation for three years, the New York Foundation for two years, and the Altman Foundation for one year. The remainder of the fund was raised by the Board of Directors of the New York Cardiac Shop. This board was created by the Board of Directors of Irvington House.

All follow-up data were obtained from the various cardiac clinics and hospitals in New York City through the efforts of Miss Claire Lingg of the New York Heart Association. In a few instances patients died and no data were obtainable. The diagnoses on death certificates were then utilized.

Thanks are due Doctor Alfred E. Cohn and Doctor Homer F. Swift for advice and criticism. I also wish to acknowledge my appreciation to the following individuals and organizations for their cooperation and interest during the investigation: Doctor Edward Holtz, Miss Dorothy Frank, Miss Katharine West; the Board of Directors of the Y. W. H. A., Mrs. Felix Warburg, chairman; the Board of Directors of Irvington House, Mrs. Louis Levy, chairman; the Board of Directors of the New York Cardiac Shop, Mrs. Jack Wildberg, chairman; and Burroughs Wellcome and Company.

rheumatic patients recently "recovered" from the disease. The cardiac disability in the younger group arises presumably from persistence of the active rheumatic process, and definite evidence of this has repeatedly been found.⁵¹⁻⁵⁴ Because of this experience this investigation was undertaken in order to learn whether active infection persists in older ambulant patients and, if so, what is its intensity and extent. With a view, furthermore, to aiding patients financially embarrassed, and to studying them under the conditions prevailing in a sheltered workshop, the New York Cardiac Shop was organized in November, 1928. The study continued until Jan. 25, 1932.

SELECTION OF CASES

Patients were referred by the hospitals and cardiac clinics in New York. At first cases classified as IIB⁵⁵ were accepted. Later when the presence of rheumatic activity in most patients became evident those in all functional classes were admitted. The 59 patients studied ranged between fifteen and forty-four years of age. They were observed from one to thirty-nine months, the average being 13.7 months. Their lesions were of the mitral or aortic valves or a combination of both. Patients suffering from syphilis were excluded.

METHODS

A history was obtained on admission. A physical examination was made at least once a week. The results were recorded on Charts 1, 2, and 3 of the New York Heart Association. The incidence and intensity of all symptoms were noted daily and recorded on a special chart. The rectal temperature was taken for five minutes and the pulse was counted for one minute daily at 10:00 A.M. and 2:00 P.M. Roentgen-ray photographs at 2-meters were taken in the anteroposterior and right antero-oblique positions; and fluoroscopic examinations of the chest in the anteroposterior and both lateral positions were made on admission and when necessary thereafter. Electrocardiograms were taken fortnightly. The leucocytes were counted weekly, between the hours of 10:30 A.M. and 12:00 noon when possible, under the same conditions as described in a previous communication.⁵⁶

EVIDENCE OF CHRONICITY

The literature concerning the value of the temperature, pulse, and leucocyte counts as indices of activity presents many conflicting opinions.

Leucocyte Count.—Swift, Miller, and Boots⁵⁷ noticed that in the continuous type of rheumatic fever in which cardiac involvement is the salient feature the count drops occasionally to normal, as in their Case 4, preceding the last cycle of fever and tachycardia before recovery. They suggested that "counts must be made frequently enough and over a sufficient period of time to set forth the trend of the leucocyte curve." Patients with marked clinical evidence of carditis exhibited the most pro-

longed leucocytosis. Thayer⁵⁸ was of the opinion that fever and leucocytosis were clear indications of carditis. According to Bezangon and Weil,⁵⁹ in uncomplicated cases of carditis of moderate severity the count was generally from 13,000 to 16,000; in milder forms slight leucocytosis was present, and in cases not accompanied by inflammatory reaction there was no leucocytosis. Bedford⁶⁰ observed in affected children no counts below 10,000 in fatal cases. Wilson and Koppel⁵² in a group ranging from four to fifteen years of age, with chronic rheumatic heart disease, frequently found leucocytosis without other evidence of infection. Findlay⁶¹ thought leucocyte counts of no value, and stated that Coombs and Perry were of like opinion.

Ernstene,⁶² in a study similar to that of Swift, Miller, and Boots,⁵⁷ concluded that the corrected sedimentation rate was a more sensitive procedure than the leucocyte count. Peterman and Seeger,⁶³ however, preferred leucocyte and differential counts particularly in showing the clinical course of the disease. Swift¹¹ regards both procedures as valuable indices.

Isolated counts are doubtless of little value, particularly in lower degrees of activity; only by making repeated counts over an extended period can the trend be properly estimated. The greater the activity the more persistent is leucocytosis. A difficulty in arriving at a judgment of the value of leucocyte counts is the marked discrepancy of opinion concerning their normal range. Swift, Miller, and Boots⁵⁷ observed the upper normal limit to be 9,000, a figure identical with my own experience,⁵⁶ allowing a 10 per cent deviation.

In this study 85 per cent of the cases showed leucocytosis, its presence ranging from 11 to 100 per cent of the total number of counts. In the entire group 2,413 counts were made, 45 per cent being above 9,000. Leucocytosis was approximately equal in frequency in cases with auricular fibrillation and in those with regular, sinus rhythm (43.9 and 46.1 per cent of the total number of counts in each group, respectively). These figures suggest the presence of an active inflammatory process, probably rheumatic in nature when viewed in conjunction with other observations.

Temperature.—Mackie²³ observed that diminished ability to exercise and the onset of cardiac failure were preceded by a rise in temperature and leucocytosis. Swift¹¹ regarded the temperature curve as probably being "the most important single index of the intensity, the spread, and the persistence of infection." Boas and Schwartz⁶⁴ observed bouts of fever in 39 cases, but Findlay⁶¹ thought it of little value as an indication of activity. Though significant, Coombs¹⁷ and Poynton⁶⁵ concluded its absence did not necessarily indicate quiescence.

Some of these differences in opinion may be explained by differences in the length of the period of study; whether the temperature was taken by mouth or rectum, and the frequency of measuring. In this study, all

the cases with two exceptions exhibited abnormal temperatures (above 99.6), ranging from one to 38 per cent of the total readings for each individual. In the entire group over 24,000 readings were made, 9.4 per cent being abnormal. The deviations were less in cases with auricular fibrillation than in those with normal sinus rhythm—4.9 and 11.6 per cent of the total readings in each group respectively. Although the elevation in temperature may be only occasional and slight, its significance is apparent when taken in relation to the pulse rate and the leucocyte count. As a sign, however, fever seems to be less valuable than leucocytosis.

Pulse Rate.—Findlay⁶¹ thought the pulse rate continued accelerated after prolonged rest in cases not developing cardiac lesions. Coombs¹⁷ also observed it during infectious activity, but was of the opinion that extra-cardiac factors may have occasioned it. When the count was elevated during sleep, Schlesinger⁶⁶ regarded it as indicative of active carditis. Allen,⁶⁷ Pichon,²⁰ and Swift¹¹ believed the sign to be of great value. Swift¹¹ stressed its importance particularly when out of proportion to the low-grade temperature in the subacute and chronic forms of the disease.

Since there are many factors which elevate the cardiac rate, I have chosen 90 beats per minute as normal and 10 per cent deviation to constitute the normal range.

Tachycardia is a valuable sign of cardiac dysfunction, particularly in this disease. Its significance, however, is limited in auricular fibrillation where digitalis is given, but its persistence after thorough use of this drug is often indicative of the presence of an acute infection. Ninety per cent of the cases with regular sinus rhythm showed tachycardia ranging from 11 to 100 per cent of the total counts. Over 16,000 counts were made, 40 per cent being abnormal.

SIGNIFICANT SIGNS AND SYMPTOMS

Dyspnea and orthopnea, palpitation, precordial pain, nausea and vomiting, rheumatic polyarthritides, twitching, nodules, muscle and joint pain, hemoptysis, diarrhea, and petechiae, are considered manifestations of activity of infection.

Dyspnea and orthopnea were present in every patient. An increase in dyspnea was very frequently the first clinical indication of beginning acute carditis. The same held true for palpitation. Precordial pain was present in 78 per cent of the cases, ranging from slight precordial distress to attacks of severe pain. Twitching was found in 22 per cent. Muscle and joint pains were both important diagnostic symptoms. In 78 per cent they occurred with considerable frequency. While it cannot be said that these pains were more frequent when rheumatic activity was great, they often appeared during periods of transition from a low to a higher degree of activity. Sometimes they were also

present as a premonitory symptom. Nausea and vomiting, independent of intoxication due to taking digitalis, were present in 75 per cent. They were often seen during acute attacks and were regarded as being indicative of activity. Diarrhea was noticed in five cases, rheumatic polyarthritis in three, and nodules in two. Hemoptysis occurred in six cases. Petechiae, similar to those found by Holtz and Friedman,⁶⁸ occurred in 83 per cent. They denote capillary permeability which is probably increased in this disease. The oral and pharyngeal lesions are often difficult to differentiate from those caused by ingestion of coarse food and are, therefore, less significant than those occurring in conjunctivae or skin. The latter appeared in 25 per cent of the cases.

The occurrence of hepatic enlargement, pulmonary râles, and edema was studied; these were undoubtedly the result of partial decompensation due to active carditis. Enlargement of the liver occurred in 80 per cent. It was found in both cases with auricular fibrillation (93 per cent) and those with regular sinus rhythm (75 per cent). Enlargement of the liver was often the only clinical evidence of a slight decompensation. Whether this phenomenon resulted directly from infection of the heart or as the result of mechanical strain, is unknown. Pulmonary râles were noticed in 59 per cent of cases with regular sinus rhythm, and in 87 per cent with auricular fibrillation. Edema was present in 32 per cent, 30 per cent when the rhythm was regular and 40 per cent in auricular fibrillation.

Valvular Lesions.—During the course of this study, in 12 patients lesions developed in valves which were previously considered sound. They made their appearance from two to seventy-eight months after the date of admission, the average being 28.5 months. The slow progress of rheumatic infection is indicated by this observation. The length of time required to be certain that this is the course of events greatly limits the opportunity to recognize many cases.

Electrocardiographic Evidence of Activity.—The criteria used in this study are those established by Cohn and Swift.¹ Abnormalities found only in Lead III, however, were excluded. A distinction was made be-

TABLE I
TRANSIENT CHANGES IN ELECTROCARDIOGRAMS

1. Increased conduction time	14 cases
2. Notching or slurring of the QRS group in 2 or more leads	1 case
3. Elevation or depression of R-T interval	16 cases
4. T-wave inversion	7 cases
5. Irregularities of rhythm	24 cases
a. Premature auricular beats	7 cases
b. Premature ventricular beats	3 cases
c. Nodal premature beats	2 cases
d. Auricular flutter	1 case
e. Auricular fibrillation	9 cases
f. Partial block	2 cases
g. Bundle-branch block	1 case

tween transient and permanent changes (Tables I and II). Those which may have resulted from taking digitalis were omitted.

TABLE II
PERMANENT CHANGES IN ELECTROCARDIOGRAMS

1. Notching or slurring of the QRS group in 2 or more leads	50 cases
2. T-wave inversion (T_1 , T_2)	6 cases
3. Auricular fibrillation	15 cases

Transient changes like those described by Cohn and Swift¹ and others,^{8, 69-73} were found in 64 per cent of cases with regular sinus rhythm, particularly with regard to the variability of the R-T segment. The observation of Levy and Turner⁷⁴ that electrocardiographic abnormalities occurred weeks and months before the onset of acute symptoms, was corroborated in this study. Of the entire group, 90 per cent exhibited permanent changes. In all cases of auricular fibrillation there were in addition notching and slurring in two or more leads.

Auricular fibrillation developed in 9 cases. The view is held by several observers⁴³⁻⁴⁶ and also by McEachern and Baker⁷⁵ that under these circumstances the walls of the auricles are invaded by rheumatic infection. High leucocyte counts have been regarded as indicative of this possibility, the rise being 24 to 100 per cent (above 50 per cent in seven cases).

Later histories were obtained in 56 cases (Tables III and IV). High leucocyte counts obtained during observation demonstrated the chronicity of rheumatic activity in this group, and suggested their significance with regard to prognosis. All but 6 patients (10 per cent) either remained stationary or became progressively worse; 26 (46 per cent) died, 18 (65 per cent of the fatalities) as a result of cardiac disease. Patients dying of cardiac failure showed similar evidence of rheumatic activity as those dying of acute carditis. Coexistence of rheumatic activity and subacute bacterial endocarditis (*Streptococcus viridans*) was observed in 3 cases.

TABLE III
FOLLOW-UP DATA THROUGH OCTOBER, 1934* (56 CASES)

FUNCTIONAL CLASSIFICATION	NUMBER OF CASES	IMPROVED	UNIMPROVED	WORSE	UNCLASSIFIED BE- CAUSE OF CARDITIS	DIED OF CARDITIS	DIED OF CARDIAC FAILURE	DIED OF SUBACUTE BACTERIAL ENDOCARDITIS	DIED FROM MISCEL- LANEOUS CAUSES
I	1	1	-	1	-	-	-	-	-
IIA	14	1	4	3	2	2	2	-	-
IIB	41	5	11	-	3	11	3	3	5
Total Number		6	15	4	5	13	5	3	5

*Based on change in functional classification.

TABLE IV

PER CENT OF ELEVATED LEUCOCYTE COUNTS DURING PERIOD OF OBSERVATION IN RELATION TO FOLLOW-UP DATA

<i>Improved</i> (6 cases)		<i>Died, carditis</i> (13 cases)	
2 cases:	none	4 cases:	3 per cent to 33 per cent
1 case :	7 per cent	5 cases:	56 per cent to 85 per cent
1 case :	30 per cent	4 cases:	100 per cent
1 case :	38 per cent		
1 case :	63 per cent	<i>Died, cardiac failure</i> (5 cases)	
<i>Unimproved</i> (15 cases)		1 case :	15 per cent
3 cases:	0 per cent to 10 per cent	1 case :	19 per cent
4 cases:	22 per cent to 30 per cent	1 case :	25 per cent
4 cases:	50 per cent to 64 per cent	1 case :	67 per cent
4 cases:	74 per cent to 100 per cent	1 case :	94 per cent
<i>Worse</i> (4 cases)		<i>Died, subacute bacterial endocarditis</i> (3 cases)	
1 case :	55 per cent	1 case :	19 per cent
1 case :	67 per cent	1 case :	55 per cent
1 case :	71 per cent	1 case :	58 per cent
1 case :	95 per cent	<i>Died, miscellaneous causes</i> (5 cases)	
<i>Unclassified, carditis</i> (5 cases)		1 case :	13 per cent
1 case :	26 per cent	1 case :	23 per cent
1 case :	33 per cent	1 case :	44 per cent
1 case :	67 per cent	1 case :	73 per cent
2 cases:	82 per cent	1 case :	100 per cent

PATHOLOGICAL ANATOMY

Four cases were studied post mortem, 3 dying of acute carditis and one of bronchopneumonia. In the former active inflammation of the various parts of the heart was demonstrated. In the fourth case, one of long standing auricular fibrillation in which activity was considered of little consequence, diffuse scarring but no cellular infiltration was found.

In one of these cases (auricular fibrillation) reactivation of the rheumatic process as demonstrated histologically was associated with signs of decompensation. Great difficulty was encountered in reducing the cardiac rate by adequate use of digitalis. The inability to do so is an important sign of active myocardial inflammation. I have observed this phenomenon repeatedly in cases with auricular fibrillation; it occurs long before the appearance of marked evidence of decompensation. When, therefore, tachycardia persists, increased administration of digitalis must be carried out cautiously as it is otherwise attended by considerable danger in acute carditis. This will be demonstrated in the case reports.

The outstanding signs, symptoms, and laboratory findings characteristic of active rheumatic infection occurring in the group are tabulated in Table V. Some cases showed only three of these features, but many showed considerably more, indicating that all cases had some degree of activity, either during observation or in the interim between the termination of the study and the follow-up period. Leucocytosis

TABLE V—CONT'D

CASE NUMBER	RHYTHM	AGE	TEMPERATURE	TACHYCARDIA	LEUCOCYTOSIS	NAUSEA AND VOMITING	DIARRHEA	PRECORDIAL PAIN	TWITCHING	MUSCLE AND JOINT PAIN	POLYARTHRITIS	NODULES	HEMOPTYSIS	PETECHIAL HEMORRHAGES	ADDITIONAL VALVULAR LESIONS	ACUTE CARDITIS	TRANSIENT CHANGES IN ELECTRO- CARDIOGRAMS	POST MORTEM
31	RSR	19	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
32	RSR	22	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
33	RSR	21	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
34	RSR	25	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
35	RSR	17	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
36	AF	16	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
37	RSR	16	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
38	RSR	17	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
39	AF	18	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
40	RSR	19	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
41	RSR	24	0	+	+	+	+	+	0	+	0	0	0	+	0	+	+	+
42	RSR	17	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
43	RSR	23	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
44	AF	36	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
45	AF	28	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
46	RSR	17	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
47	RSR	17	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
48	RSR	17	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
49	AF	28	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
50	RSR	26	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
51	AF	20	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
52	RSR	16	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
53	AF	24	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
54	RSR	17	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
55	RSR	23	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
56	RSR	27	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
57	AF	44	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
58	AF	17	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+
59	RSR	18	+	+	+	+	0	+	0	+	0	0	0	+	0	+	+	+

+ = present

0 = absent

- = indeterminate

was by far the most prominent sign in recognizing rheumatic activity regardless of rhythm; muscle and joint pain, and precordial pain were next in importance; tachycardia and transient changes in the electrocardiogram were very valuable signs in the group with regular sinus rhythm. Although abnormal temperature occurred in all but one case, it did not occur with sufficient regularity in many to be considered as important as those signs already mentioned.

CASE REPORTS

Several cases, both of regular sinus rhythm and of auricular fibrillation, exhibiting various types of activity are discussed in detail in the following case reports. Although Pichon,²⁰ on the basis of clinical observations, classified rheumatic activity into two types, (a) an evolutive or chronic form (not a cicatricial one in which the process has stopped), and (b) acute pancarditis, it is my opinion that the difference is one of degree only.

CASE 30.—E. L., aged seventeen years, was admitted to the Cardiac Shop Sept. 5, 1930. The diagnosis was rheumatic mitral stenosis and insufficiency, enlarged heart; the rhythm was regular, and her functional classification IIA. Cardiac symptoms were observed by the patient one year prior to the onset of rheumatic fever. Her illness began with an attack of tonsillitis followed by rheumatic polyarthritis in the Spring of 1930. Fever, tachycardia, and leucocytosis persisted throughout the period of observation (Fig. 1). Bouts of acute carditis occurred in December, 1930, and October, 1931: the first was associated with symptoms of nausea, vomiting, increasing dyspnea, orthopnea and cough, the second was preceded by an upper respiratory infection. There were periods, which often coincided with increased cardiac reserve, when the leucocyte curve approached the normal level, but quiescence was never attained. Cardiac reserve diminished when rheumatic activity increased, as shown by the two bouts of acute carditis. She was observed until Jan. 25, 1932, a period of seventeen months. During July and August, 1934, "she was confined to a hospital. Diagnosis: *active carditis*, mitral stenosis and insufficiency, *aortic insufficiency*, regular sinus rhythm, *no classification because of rheumatic activity.*"

CASE 36.—J. O'D., aged sixteen years, was admitted to the Cardiac Shop May 22, 1929. The diagnosis was rheumatic mitral stenosis and insufficiency, enlarged heart, auricular fibrillation, Class IIB. At the age of three years, tonsillectomy was performed. The presence of heart disease was discovered at the age of six years during a routine physical examination. At twelve years, she suffered an attack of rheumatic polyarthritis, when cardiac symptoms were first experienced. Low-grade fever, occasional periods of tachycardia, pulse deficit, and persistent leucocytosis were present (Fig. 2). Frequent bouts of acute carditis made the problem of giving digitalis difficult. The maintenance dose was not increased so that toxic manifestations, often similar to the symptoms of the disease, might be avoided. Rest in bed was often sufficient to bring about a state of improvement. The first bout of carditis observed occurred in September, 1929, and was associated with diarrhea, vomiting and palpitation. The second, December, 1929, preceded by an upper respiratory infection, was associated with slight edema of the ankles. The third, October, 1930, was associated with pains in the knees and cyanosis of the lips. The fourth occurred

in February, 1931, accompanied by pains in her joints. Rheumatic nodules were noticed in March, 1931. The fifth bout occurred in April, 1931. After treatment in a hospital and care in a convalescent home the patient returned in August, 1931, much improved. She was studied until Jan. 25, 1932, a period of thirty-two months. On March 5, 1934, "her left hand was swollen and painful, nodules appeared on ankles and elbows. The diagnosis was mitral stenosis and insufficiency, auricular fibrillation, not classified because of rheumatic activity."

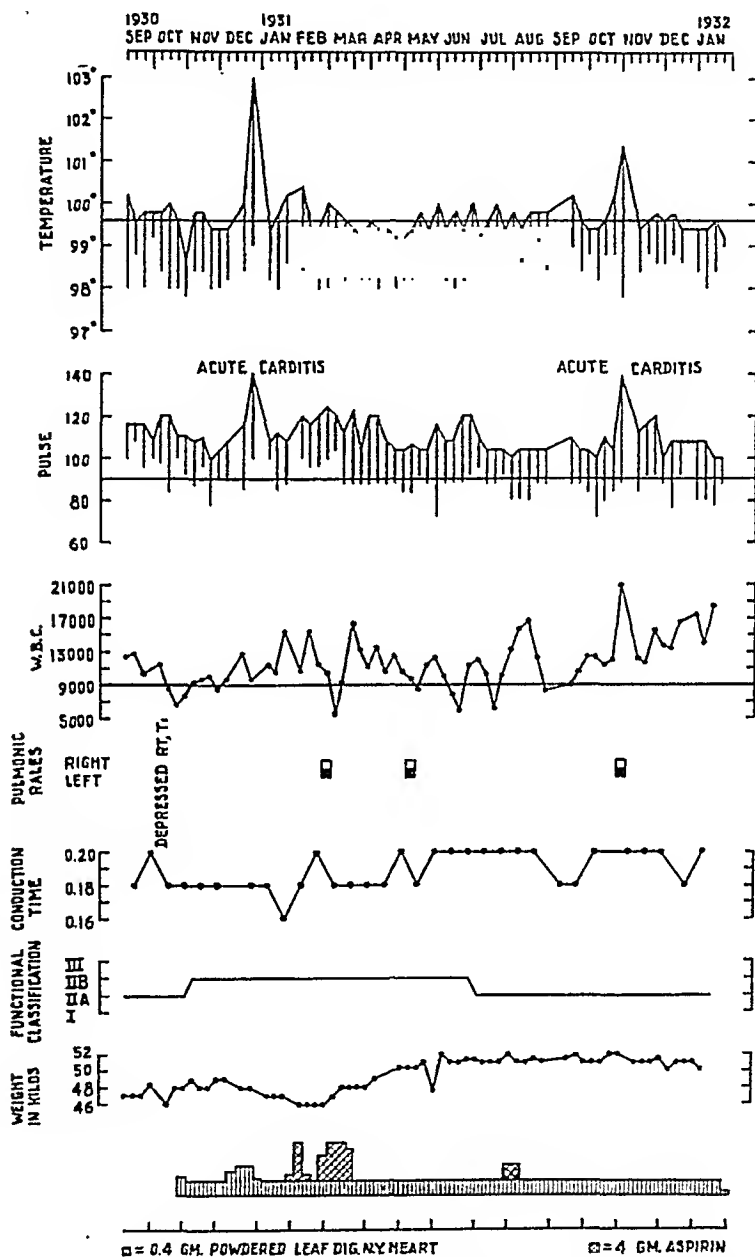


Fig. 1.—Each space indicated on the top contains the data collected during one week. The high and low pulse counts and temperature readings for each week are indicated by vertical lines. The highest weekly pulse counts and temperature readings are joined by continuous lines. In cases of auricular fibrillation the pulse deficit is represented by shaded areas, its absence by a single continuous line. The weekly white cell count is recorded by connecting lines.

These two cases illustrate a continuous type of activity lasting for years, with bouts of acute carditis occurring with equal intensity both when the rhythm was regular and during auricular fibrillation. The bouts were probably accentuated manifestations of a preexisting active rheumatic state.

CASE 6.—H. B., aged nineteen years, was admitted to the Cardiac Shop Nov. 3, 1928. The diagnosis was rheumatic mitral stenosis and insufficiency, enlarged heart, regular sinus rhythm, Class IIB. Tonsillectomy was performed at six years of age. She was seized with chorea at eleven years, when the presence of heart disease was discovered. Cardiac symptoms were first observed by the patient the following year during a period of fever. Persistent low-grade fever, tachycardia and leucocytosis were observed (Fig. 3). The first bout of acute carditis occurred in April, 1929,

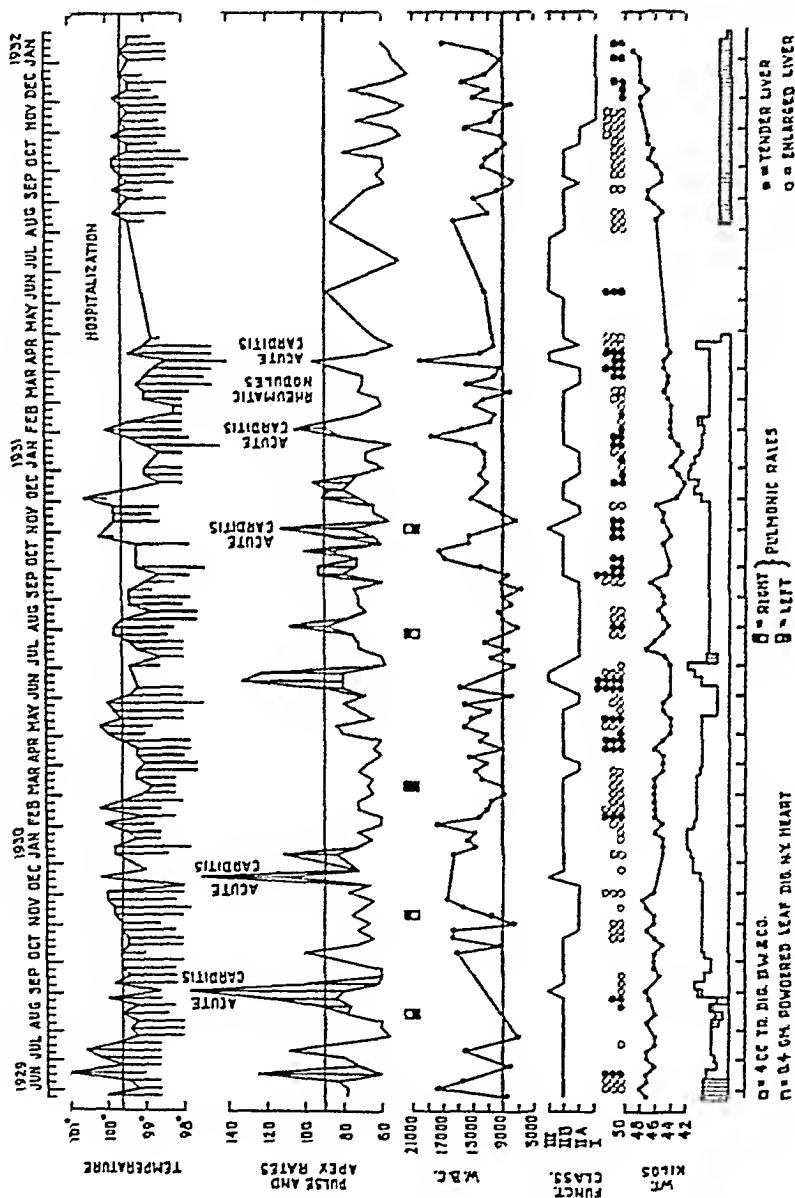


FIG. 2.—Each space indicated on the top contains the data collected during one week. The high and low pulse counts and temperature readings for each week are indicated by vertical lines. The highest weekly pulse counts and temperature readings are joined by continuous lines. In cases of auricular fibrillation the pulse deficit is represented by shaded areas, its absence by a single continuous line. The weekly white cell count is recorded by connecting lines.

associated with increase in the degree of her cardiac symptoms and the first appearance of premature auricular beats. From September, 1929, through November, 1929, she was confined to her home during the second attack of acute carditis. In December, 1929 she contracted acute bronchopneumonia. Premature auricular beats began to increase in number and in the latter part of February, 1930, gallop rhythm was observed. Digitalis was given, but the persistence of the symptoms necessitated complete rest. In March, 1930, slight pitting edema of the legs was noticed. Dyspnea, nausea, vomiting, and diarrhea were also present; they were at-

tributed to acute carditis and not to digitalis intoxication. On Aug. 14, 1930, during the third period of acute carditis, auricular fibrillation supervened. In May, 1931, following severe infection of the upper respiratory tract, a fourth bout occurred associated with cough and vomiting. The temperature, apex rate, and leucocyte counts

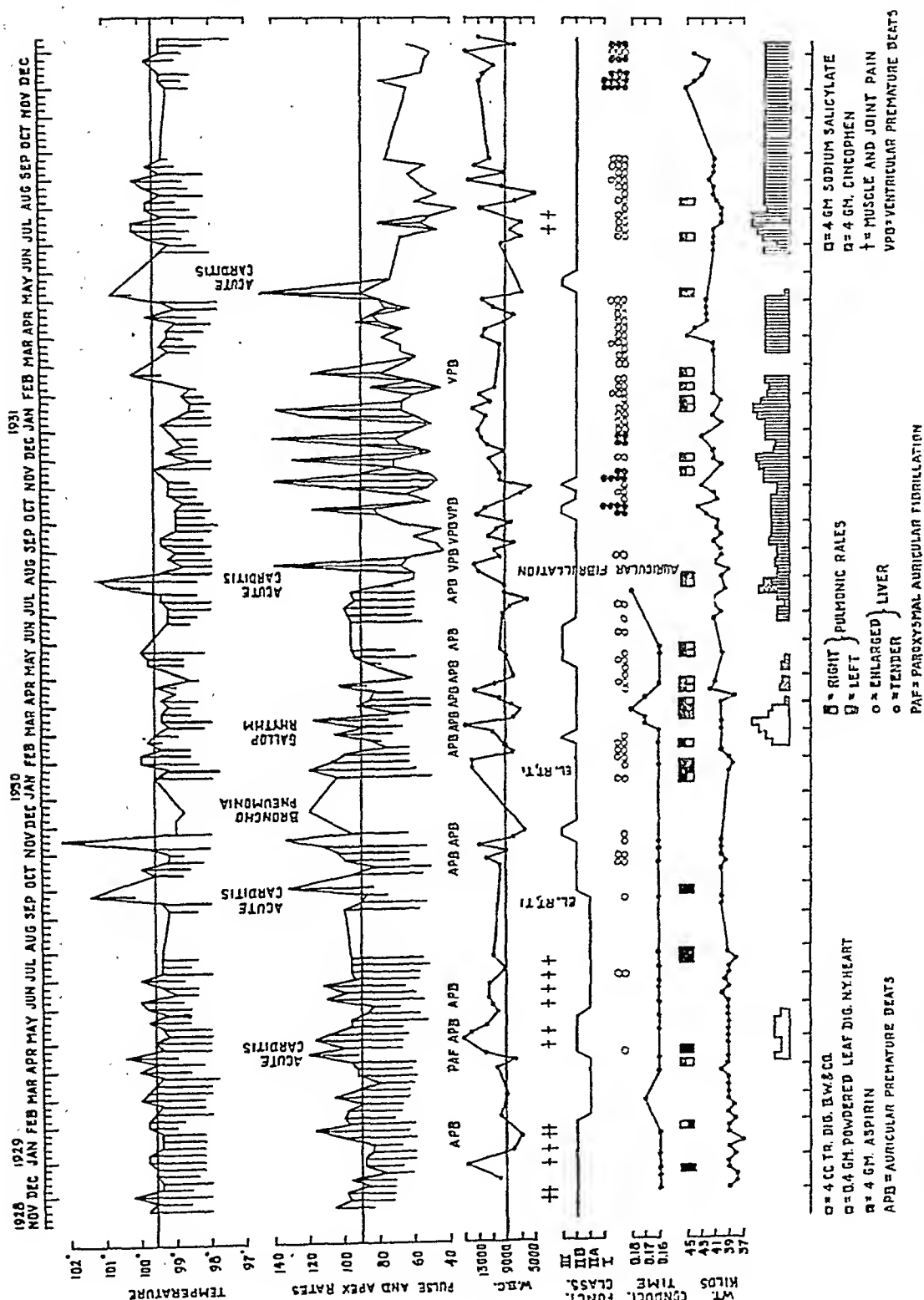


FIG. 3.—Each space indicated on the top contains the data collected during one week. The high and low pulse counts and temperature readings for each week are indicated by vertical lines. The highest weekly pulse counts and temperature readings are joined by continuous lines. In cases of auricular fibrillation the pulse deficit is represented by shaded areas, its absence by a single continuous line. The weekly white cell count is recorded by connecting lines.

rose, and the severity of her cardiac symptoms increased. The patient was confined to bed in a hospital for one month. In October, 1931, she was sent to a convalescent home for two months and returned much improved. She was observed until Jan. 25, 1932, a period of thirty-nine months. On Oct. 8, 1934, the diagnosis was "mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation, Class IIB."

In this case, the occurrence of auricular fibrillation is exhibited during a period of acute carditis and the continuance of rheumatic activity in the same state of intensity after the change of rhythm.

CASE 25.—S. K., aged sixteen years, was admitted to the Cardiac Shop Jan. 13, 1930. The diagnosis was rheumatic mitral stenosis and insufficiency, enlarged heart, regular sinus rhythm, Class IIB. There was no history of polyarthrititis, chorea, or tonsillitis. Her tonsils were removed at six and at thirteen years of age. The existence of heart disease was discovered at the age of eight years. The first cardiac symptoms, together with chills, fever, palpitation, and dyspnea, appeared in 1929. The temperature, pulse, and leucocyte curves showed cyclic periods of fever, tachycardia, and leucocytosis (Fig. 4). An elevation of the three curves during July, 1930,

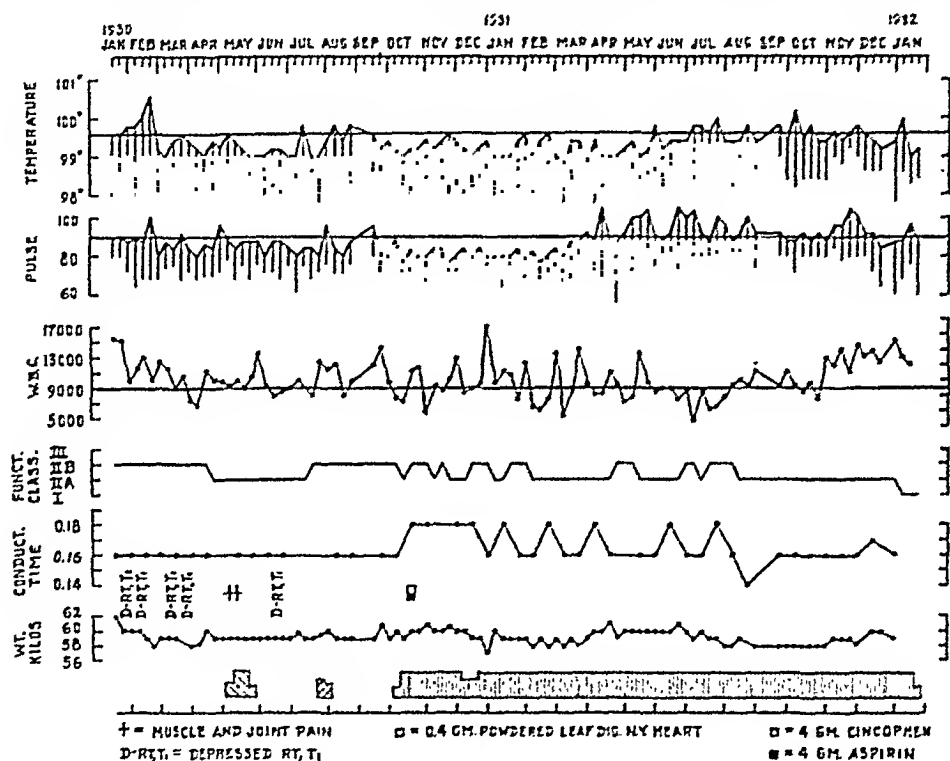


Fig. 4.—Each space indicated on the top contains the data collected during one week. The high and low pulse counts and temperature readings for each week are indicated by vertical lines. The highest weekly pulse counts and temperature readings are joined by continuous lines. In cases of auricular fibrillation the pulse deficit is represented by shaded areas, its absence by a single continuous line. The weekly white cell count is recorded by connecting lines.

was associated with increased dyspnea. The symptoms, however, did not reach sufficient proportions to be considered those of acute carditis. Regardless of improvement (Class I) during January, 1932, the evidence revealed persistent rheumatic activity. She was observed until Jan. 25, 1932, a period of twenty-four months. On Oct. 22, 1934, she complained of "palpitation, dyspnea, orthopnea, occasional cardiac pain, feeling of oppression over precordium. The diagnosis was rheumatic mitral stenosis and insufficiency, *auricular fibrillation*, Class IIB."

CASE 12.—J. DeJ., aged eighteen years, was admitted to the Cardiac Shop July 11, 1929. The diagnosis was rheumatic mitral stenosis and insufficiency, enlarged heart, *auricular fibrillation*, Class IIA. There was no history of polyarthrititis or

chorea. The presence of heart disease was discovered at eleven years. An attack of tonsillitis had occurred at twelve years; the tonsils were removed at thirteen. Cardiac symptoms began to be noticed at thirteen years, when irregular palpitation was felt and digitalis was given. Irregular periods were observed of low-grade fever and leucocytosis, the latter being the more pronounced (Fig. 5). The cardiac rate was lowered by taking digitalis. The course of this patient was complicated by the occurrence of amenorrhea from May until August, 1931, and later by metrorrhagia,

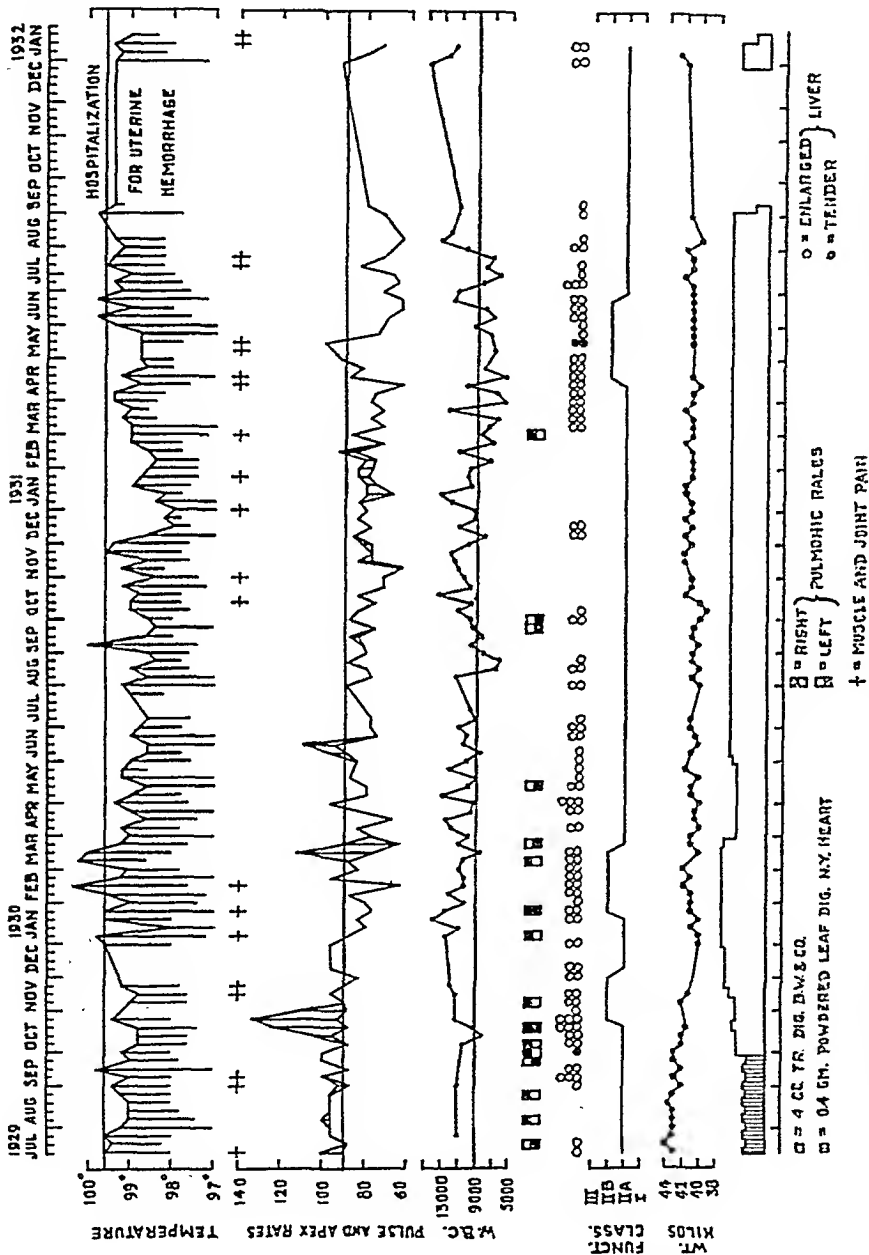


Fig. 5.—Each space indicated on the top contains the data collected during one week. The high and low pulse counts and temperature readings for each week are indicated by vertical lines. The highest weekly pulse counts and temperature readings are joined by continuous lines. In cases of auricular fibrillation the pulse deficit is represented by shaded areas, its absence by a single continuous line. The weekly white cell count is recorded by connecting lines.

lasting three weeks and causing secondary anemia, severe enough to necessitate transfusion of blood. She was observed until Jan. 25, 1932, a period of thirty-one months. On Oct. 16, 1934, she was "feeling ill, complaining of nausea, fatigue, dyspnea, cough, and palpitation. The diagnosis was rheumatic mitral stenosis and insufficiency, auricular fibrillation, Class IIB."

These two cases presented the same degree of rheumatic activity when the rhythm was regular and when auricular fibrillation was pres-

ent. There was evidence of alternating rheumatic activity and latency. Cardiac reserve was not so much diminished nor did the activity assume such proportions as would suggest the presence of acute carditis. The use of digitalis was also a much simpler problem than in the previous group.

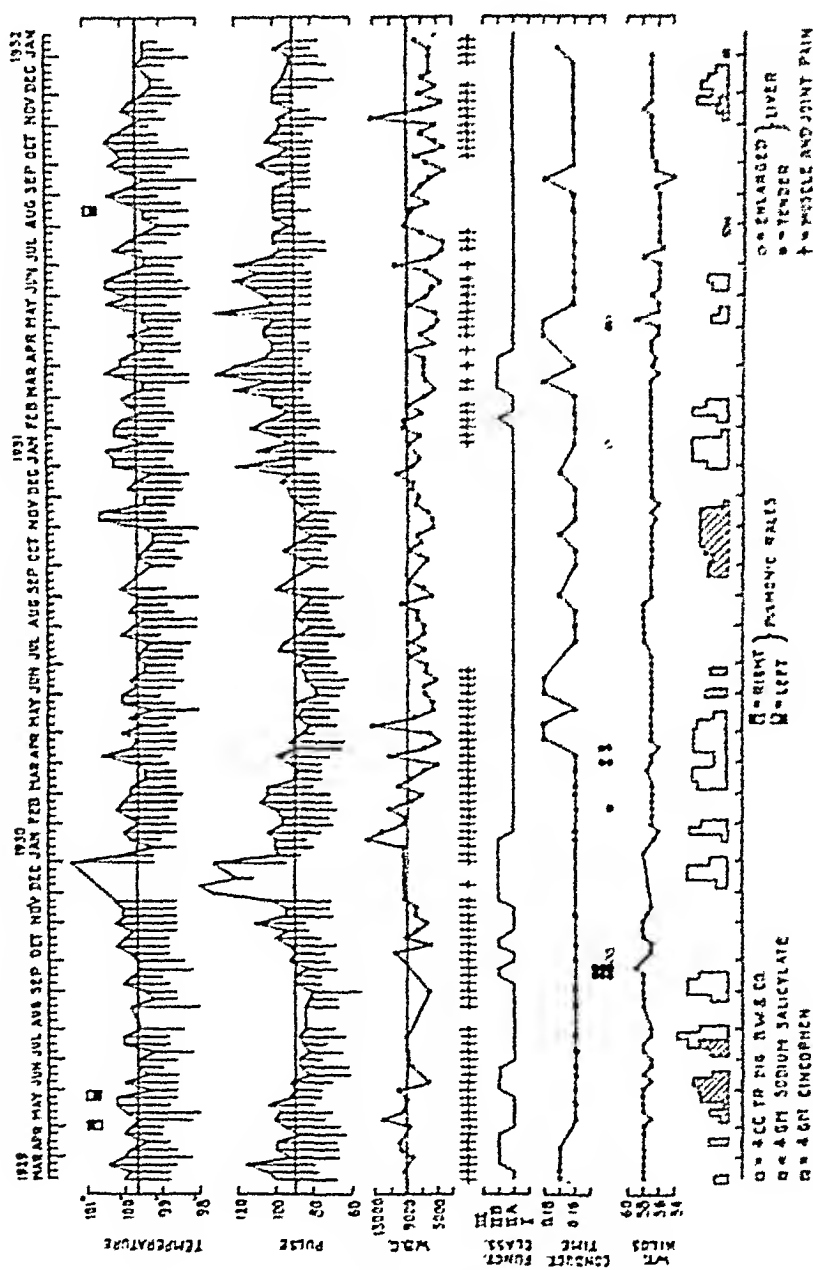


Fig. 6.—Each space indicated on the top contains the data collected during one week. The high and low pulse counts and temperature readings for each week are indicated by vertical lines. The highest weekly pulse counts and temperature readings are joined by continuous lines. In cases of auricular fibrillation the pulse deficit is represented by shaded areas, its absence by a single continuous line. The weekly white cell count is recorded by connecting lines.

CASE 55.—G. S., aged twenty-three years, was admitted to the Cardiac Shop March 12, 1929. The diagnosis was rheumatic mitral stenosis and insufficiency, enlarged heart, regular sinus rhythm, Class IIA. She suffered an attack of tonsillitis at seventeen years, the tonsils were removed at eighteen, heart disease was discovered at nineteen with the onset of cardiac symptoms; an attack of rheumatic polyarthrititis occurred at twenty-one. The pulse rate, temperature, and leucocyte curves ran a more or less parallel course, being elevated from March, 1929, to May, 1930 (Fig. 6). The

leucocyte curve then reached a normal level with only a rare count above 9,000. The other curves fluctuated, however, showing occasional periods of tachycardia and slight fever, particularly between November, 1930, and the termination of the study. The chief complaints were frequent pains in muscles and joints. During December, 1930, the severity of her cardiac symptoms increased. She was observed until Jan. 25, 1932, a period of thirty-four months. On Oct. 8, 1934, she was "feeling ill, complained of pains in arms and legs, fatigue, dyspnea, occasional palpitation. The diagnosis was rheumatic mitral stenosis and insufficiency, regular sinus rhythm, Class IIA."

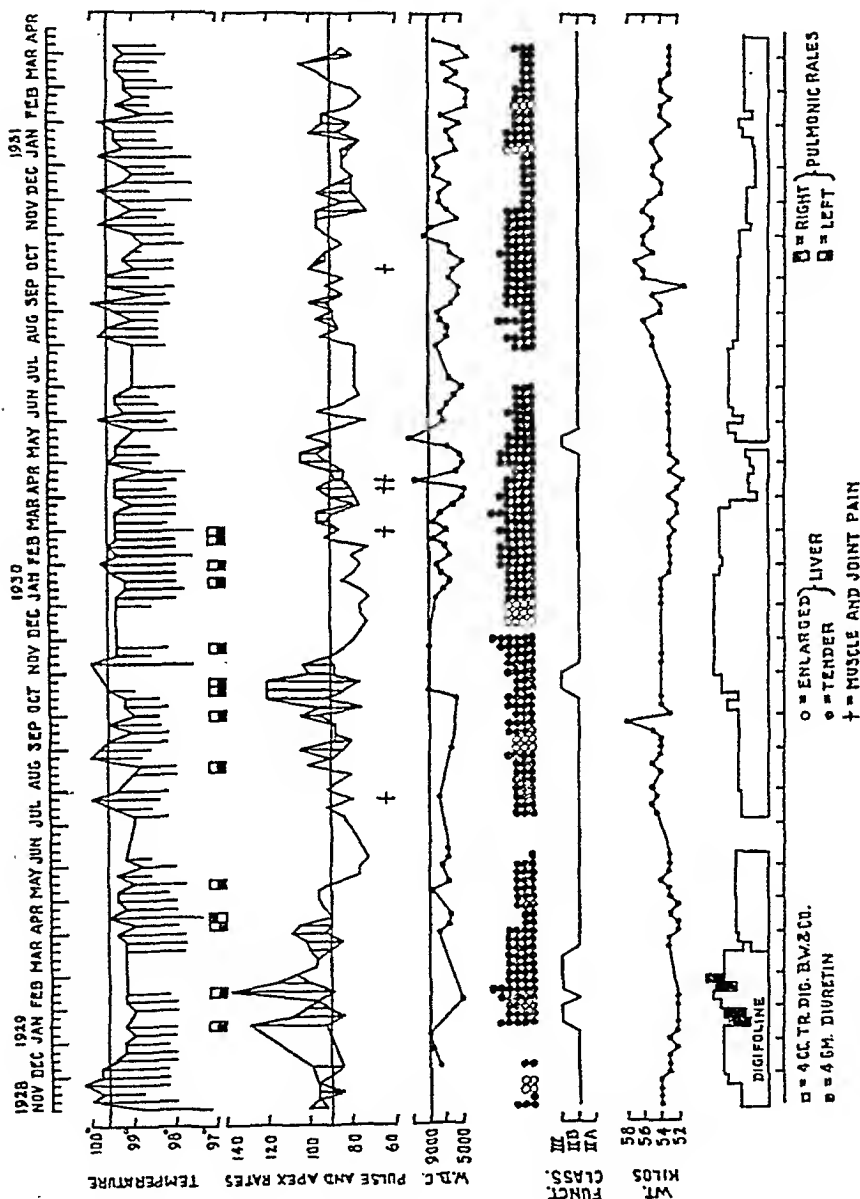


Fig. 7.—Each space indicated on the top contains the data collected during one week. The high and low pulse counts and temperature readings for each week are indicated by vertical lines. The highest weekly pulse counts and temperature readings are joined by continuous lines. In cases of auricular fibrillation the pulse deficit is represented by shaded areas, its absence by a single continuous line. The weekly white cell count is recorded by connecting lines.

This case is an example of the type in which long periods of quiescence are interrupted by periods of slight rheumatic activity, more apparent from the pulse and temperature curves than from the leucocyte curve.

CASE 8.—C. B., aged thirty years, was admitted to the Cardiac Shop Nov. 3, 1928. The diagnosis was rheumatic mitral stenosis and insufficiency, enlarged heart, auricular fibrillation, Class IIB. An attack of rheumatic polyarthrits occurred at the age of twenty, when the existence of heart disease was discovered. Cardiac symptoms appeared first at twenty-three, with the onset of irregular palpitation and decom-

pensation. Throughout the entire course of study, a few leucocyte counts only were above 9,000 (Fig. 7). There was an occasional rise in temperature not associated with pulse deficits. She complained at times of muscle and joint pains. The chief difficulty in treatment consisted in finding the correct dose of digitalis. She was observed until April 17, 1931, a period of thirty months. On Aug. 27, 1934, "the diagnosis was rheumatic mitral stenosis and insufficiency, *aortic insufficiency*, auricular fibrillation, Class IIB."

This case illustrates a grade of rheumatic activity so low that its presence cannot be demonstrated by usual methods. Nevertheless, after a period of six years, the involvement of an additional valve became apparent. In all probability the process was fibrotic, slow in growth, rather than inflammatory.

In the next case, rheumatic activity was known to exist for three months prior to the onset of cardiac symptoms. It is included to show the compatibility of rheumatic activity with normal physical capacity.

CASE 13.—L. D., aged seventeen years, was admitted to the Cardiac Shop Oct. 7, 1931. The diagnosis was rheumatic mitral stenosis and insufficiency, aortic stenosis and insufficiency, enlarged heart, regular sinus rhythm, Class I. An attack of tonsillitis occurred at nine years, heart disease was discovered at ten years, and an attack of chorea took place at eleven years. The history of this case suggests an intermittent type of activity. Cardiac symptoms first appeared at the end of the study. She was observed until Jan. 15, 1932, a period of three months. On Aug. 16, 1934, a history was obtained of "*epistaxis, hemoptysis, palpitation, precordial pain, pain in elbows and wrists*. She was sleeping on three pillows. The diagnosis was rheumatic mitral stenosis and insufficiency, aortic stenosis and insufficiency, *sinus tachycardia*, Class IIB."

This is the type of case which explains the presence of rheumatic inflammation frequently found post mortem when it was not suspected during life.

The chronicity of infection, exhibited by these cases emphasizes the similarity between chronic rheumatic cardiac disease and chronic pulmonary tuberculosis, frequently referred to by other observers.^{17, 76} In both maladies recrudescence may be expected even in the absence of objective signs of activity. Evidence suggested that rheumatic activity ranged from being quiescent, with occasional periods of recrudescence, to being continuous, with bouts of acute carditis, leading in each instance to further damage to the heart. The present use of the term "carditis," limited as it is to frankly acute exacerbations with obvious signs and symptoms, is erroneous and misleading. The data reveal unquestionable evidence of mild acute carditis long before a typical "attack" supervenes.

SUMMARY

1. Information was collected on 59 ambulatory cases of chronic rheumatic cardiac disease by obtaining at suitable intervals, histories, symptoms, leucocyte counts, pulse rates, measurements of temperature, physical examinations, electrocardiograms, x-ray photographs of the

heart, and post-mortem reports. The group consisted of women between the ages of fifteen and forty-four years who were studied for a period of one to thirty-nine months, the average being 13.7 months.

2. Rheumatic infection was probably active in each case either during observation or later.

3. The most valuable single procedure for ascertaining the presence of rheumatic activity was the leucocyte count. Leucocytosis occurred in 85 per cent of the cases, its presence ranging from 11 to 100 per cent of the total number of counts.

4. In some cases the rheumatic process appeared to be (a) either relatively quiescent or only slightly active, (b) in others, periods of inactivity alternated with others of activity, and (c) finally there were those in which activity was more or less continuous. These types occurred with equal frequency whether the rhythm was regular or there was auricular fibrillation.

5. Patients manifesting frank signs and symptoms of acute carditis showed evidence of having had a preexisting active rheumatic state.

6. Whether death occurred as the result of cardiac failure or of acute carditis, similar evidence of rheumatic activity was found.

7. In three patients rheumatic activity and subacute bacterial endocarditis coexisted.

8. The regular sinus rhythm gave way to auricular fibrillation in nine cases. In each instance the irregularity supervened during periods of rheumatic activity.

9. In several cases, rheumatic activity continued for several years, leading to progressive cardiac damage and diminished cardiac reserve.

10. In certain cases rheumatic activity is at times compatible with normal cardiac reserve.

CONCLUSION

In this study it is shown that in many adult cases of rheumatic heart disease prolonged and progressive active infection persists, sometimes so mild as to be scarcely detectable, but sometimes exhibiting high grades of severity.

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THE PRECIPITATING CAUSES OF CONGESTIVE HEART FAILURE*†

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THE importance of added strain in the precipitation of congestive failure in an overburdened heart has long been recognized. White¹ states that "in a person with heart disease, failure is often precipitated by a relatively trivial circumstance, such as a slight respiratory infection, overeating, or slight overexertion, but usually heart failure is of gradual onset without any particular precipitating factor. In children, acute rheumatic infection is the most frequent immediate cause." Herrmann² states that "the establishment of a precipitating factor is of significance in the prognosis and future management of any patient with cardiovascular breakdown." Cowan and Ritchie³ list the following causes: exercise, pregnancy, hemorrhage, pulmonary infection, emphysema, gastrointestinal disturbances which produce disturbances in nutrition, intoxication, operation, mental shock, starvation in any form, acute exacerbation of chronic renal disease, and surgical shock. This list, of course, is only partial. The number of precipitating causes is limited only by the number of factors capable of causing cardiac or circulatory strain. Donzelot⁴ has given a detailed survey of the cardiac and extracardiac conditions responsible for heart failure, but has reported no cases. Davis⁵ has considered the traumatic causes.

In a search of the literature we were unable to find a series of consecutive cases of congestive heart failure in which the precipitating cause of the attack had been used to prognosticate the outcome from that attack. Likewise, we were unable to find a consecutive series in which the relative frequency of the precipitating causes had been analyzed. A review of the routine ward histories also indicated that the events leading to the development of congestive failure are not always recorded. These facts prompted us to investigate this problem and necessitated a detailed questioning of each patient regarding the onset of congestive failure.

We have attempted to elicit the precipitating causes in 100 consecutive patients with congestive heart failure entering the Tulane Medical Service of Charity Hospital and the Hutchinson Memorial Clinic during the autumn of 1936. Each patient has been carefully questioned, examined and followed by both of us. All were bedridden. Diagnoses

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were made according to the criteria approved by the American Heart Association, and treatment, including bed rest, digitalization, sedatives, and symptomatic measures, while varying with the patient, was comparable in indications and application.

TABLE I
ETIOLOGY OF HEART DISEASE

Hypertension and arteriosclerosis	30
Arteriosclerosis	27
Hypertension	25
Luetic heart disease	10
Rheumatic heart disease	7
Congenital	1
Total	100

The diagnoses as to etiological types are recorded in Table I. Hypertension and arteriosclerosis, separately or in combination, accounted for over 75 per cent of the group; syphilis for 10 per cent; rheumatic fever for 7 per cent, and congenital anomalies for 1 per cent. This distribution is representative of the general incidence of the etiological types of heart disease in our service.

In the majority of cases a precipitating cause was definitely demonstrable. In three individuals, in subsequent attacks, a different precipitating cause was apparent, so that 104 instances were recorded for the 100 individuals. They were distributed as follows: exercise 20; infection (upper respiratory tract 15, acute gastroenteritis 1, acute bacillary dysentery 1, erysipelas 1) 18; pregnancy 5; surgical shock 2; coitus 2; sudden rise in blood pressure 2; psychic trauma 2; hemorrhage 2; heavy meal 1; and alcoholism 1. A gradual onset occurred in 47 patients without demonstrable cause, and an acute onset in two patients, cause not definitely known, but probably a sudden rise in blood pressure. In the 47 patients with gradual onset, 46 were unable with treatment to compensate sufficiently to carry on minimal normal activity. Among those in whom precipitating causes were demonstrable, in 40 compensation was established rapidly and sufficiently under treatment to make the patient able to carry on usual activity, 14 failed to show compensation to that extent, and 3 could not be followed.

DISCUSSION

Contrary to the views expressed in the literature, in our series over 50 per cent of the patients had a definite precipitating factor leading to the development of congestive failure. Had we been able to elicit a satisfactory history in every case, particularly in those of long standing, the percentage might have been higher. Again, precipitating causes may have been present but not evident to the patient. Even a careful history would fail to elicit them.

The relative frequency of the precipitating factors would doubtless vary in any series with the race, age, and sex of the patients, climatic conditions of the particular area, the season of the year, and any other conditions which vary the incidence of disease and the occupations and habits of the patients. Although these factors may influence the relative frequency of the precipitating causes of heart failure and of heart failure itself, we were unable to demonstrate the influence of any of these factors upon the ability or inability of the patients in our group to re-establish compensation. Such data are of great importance and can be obtained only by the comparison of entire groups similar to this one.

As mentioned previously, a gradual onset of congestive failure occurred in 47 patients without demonstrable precipitating cause. That 46 of these individuals were unable to compensate sufficiently to carry on minimal activity is strikingly evident and points out clearly the value of the determination of the type of onset in prognosis. Such patients usually developed evening edema which became progressively worse for a varying period of time until they were bedridden. It appears that these patients had had no forewarning of the progressive diminution in their cardiac reserve until it was so diminished that even minimal activity exceeded it. However, had such a patient a warning of diminishing cardiac reserve by a precipitating factor before this limit were reached, he probably would have reacted to treatment and would have been able to adjust his activity to meet his existing cardiac reserve. Furthermore, treatment of any correctible etiological factor could have been instituted to prevent further encroachment upon the heart. These statements are borne out by the progress of our cases with a known precipitating cause. In 40 of the 57 instances with a known precipitating cause the patients compensated rapidly with treatment and sufficiently to carry on usual activities. Fourteen failed to compensate to that extent and 3 could not be followed. Four of the 14 patients had syphilitic aortic regurgitation, while in the group with ability to compensate there were none with this condition. It is possible that in the remaining 10 instances the patients were already on the verge of failure when the precipitating cause intervened. Omitting the 4 patients with syphilitic aortic regurgitation, who seem to form a special group, the patients with distinct precipitating causes had a 75 per cent chance of recovering compensation; those without a known precipitating cause over 95 per cent chance of not recovering compensation.

Infection and exercise are the usual precipitating causes emphasized in the literature. In our series these constituted 38 of the 55 instances of known precipitating causes. Even though these factors may be helpful in diagnosis, and later in prognosis, in patients with heart disease, they are always detrimental and should be avoided.

The 5 patients with pregnancy as a precipitating cause deserve special consideration. Three of these developed congestive failure in the third

trimester. They represent the usual type of patient with congestive failure precipitated by the increased strain of pregnancy. All three of these patients reestablished compensation satisfactorily following delivery. The remaining two are representative of a group in which congestive failure occurs post partum. A search of the literature indicates that cardiac decompensation at that time is most unusual in the absence of vascular complications. In our patients congestive failure was absent during pregnancy and developed for the first time in the puerperal period within three weeks following delivery. We see in these patients the remarkable fact that congestive failure occurred for the first time after the release of the usual strain of pregnancy upon the heart. The history, course, and physical findings make up a characteristic picture, but the mechanism by which failure was precipitated is not clearly understood. A series of patients of this type and the possible mechanisms involved are described in detail elsewhere.⁶ One of the two patients in the present series died in heart failure. The other is living but has failed to compensate sufficiently to carry on minimal activity.

Two patients with hypertension, followed before the onset of congestive failure, developed decompensation immediately after a sudden rise in blood pressure. The cause of the rise in the pressure could not be determined. No other possible precipitating causes could be elicited at that time. This evidence strongly suggests that the sudden rise in blood pressure precipitated the failure. With a reduction in blood pressure to the former level compensation was reestablished. Two other patients not followed before the development of congestive failure, and without any known precipitating cause, displayed the same picture. These patients are listed in Table II as sudden onset of unknown cause.

TABLE II
PRECIPITATING CAUSES OF CONGESTIVE HEART FAILURE

CAUSE	INCIDENCE	NUMBER COMPENSATED WITH TREATMENT	NUMBER NOT COMPENSATED WITH TREATMENT
Gradual onset (cause unknown)	47	1	46
Infection	18	12	6
Exercise	20	14	6
Pregnancy	5	3	2
Sudden rise in blood pressure	2	2	0
Sudden onset (cause unknown)	2	2	0
Psychic trauma	2	1	1
Hemorrhage	2	1	1
Surgical shock	2	1	1
Coitus	2	2	0
Heavy meal	1	1	0
Alcoholism	1	1	0
Total	104	41	63

A sudden rise in blood pressure suggests itself as the precipitating cause in these patients. Since a sudden rise in blood pressure may be asymptomatic, it is possible that it may be active as a precipitating cause with no evidence in the history.

The mechanisms of psychic trauma, hemorrhage, postoperative shock, coitus, overeating, and alcoholism as precipitating causes of congestive failure are self-evident.

The importance of the etiological diagnosis in predicting the outcome in the presence or absence of a precipitating cause was considered. It was found to be a factor in those with syphilitic aortic regurgitation. In these patients the prognosis was poor regardless of the precipitating cause. These observations are in keeping with the usual grave prognosis given such patients when cardiac compensation has once been broken.

It is stated in the literature that active rheumatic carditis is often a precipitating cause of congestive failure in patients with chronic rheumatic endocarditis. In our seven patients signs of active rheumatic fever could not be elicited. Furthermore, three of these patients had a definite precipitating cause unrelated to rheumatic fever. The remaining four had a gradual onset without any demonstrable precipitating cause. It is possible that an unrecognized active carditis may have played a rôle in the development of failure in these patients.

SUMMARY AND CONCLUSIONS

A study of 100 consecutive cases of congestive heart failure indicates that:

1. In 55 (52.9 per cent) of 104 instances of congestive failure a definite precipitating cause was demonstrable.
2. The reaction to therapy was poor following congestive heart failure with a gradual onset without demonstrable precipitating cause. Over 95 per cent of these patients failed to compensate sufficiently to carry on minimal activity.
3. We were usually able to prognosticate a good response to treatment in patients with a definite precipitating cause provided the cause could be removed. In 75 per cent of these patients removal of the precipitating cause fostered rapid and sufficient recovery of cardiac reserve to permit at least minimal activity.
4. The precipitation of congestive heart failure by a factor putting a strain on the heart acts as a forewarning of the existence of lowered cardiac reserve so that with treatment and adaptation the patient's life may be prolonged. Such a factor, however, is always detrimental to the heart.

5. Following congestive failure patients with syphilitic heart disease with aortic regurgitation showed an inability to compensate regardless of the precipitating cause. The etiological diagnosis otherwise was not found to be significant.

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RELATION OF MYOCARDIAL DISEASE TO ABNORMALITIES OF THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM*†

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THE finding of an abnormal ventricular complex in the electrocardiogram is commonly used as a basis for the diagnosis of myocardial disease, but discrepancies between the electrocardiographic diagnosis and autopsy findings have occasionally been reported. It seems worth while therefore to review a considerable number of cases with the idea of determining the reliability of electrocardiographic evidence in diagnosing the presence or absence of morphological changes in the ventricular myocardium. Sixty cases have been selected for this study. The records of all autopsies performed at the New York Hospital between Sept. 20, 1930 and July 4, 1932, were reviewed, including cases from both the medical and the surgical services. Those cases were selected for study that had electrocardiographic records made shortly before death and had neither received digitalis nor quinidine recently enough for these to have influenced the record. Only the standard leads were obtained in these cases.

The electrocardiographic record was considered abnormal when those features were discovered in the ventricular waves which have been commonly considered to indicate myocardial disease. These are as follows: duration of QRS exceeding 0.10 seconds; notching or slurring of QRS near the peak of a large wave and in more than one lead of the record; voltage of the QRS group less than 5 mm.; Q_3 measuring more than 25 per cent of the largest excursion of QRS excepting in the presence of right axis deviation; R-T or S-T junction occurring more than 1 mm. above or below the P-R level; diphasic, isoelectric or downward T-waves in Leads I or II or in both; significant changes in the voltage or other features of the QRS or T-waves observed in records of the same patient taken a few days from one another.

It is to be emphasized that only when these features were quite definite have they been made the basis of a diagnosis of *abnormal ventricular complex*. Notching and slurring were especially carefully scrutinized and were not considered positive unless evident in two leads and in one of these involving a part of QRS remote from the base line. When the

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complex was such as to indicate bundle-branch block it was not also considered under the categories of notched, wide QRS or inverted T, even though these features might have been present.

Auricular fibrillation, auricular flutter, and heart block have been omitted from this list of electrocardiographic abnormalities. This has been done because, though these physiological disturbances often have a basis in structural myocardial disease, yet such changes would be expected in the auricles or in the A-V conduction system and not in the ventricular myocardium, which alone has been subjected to careful pathological study. Premature beats and paroxysmal tachycardia may also arise because of structural myocardial disease but they may so often be neurogenic in origin that it was not considered proper to attempt to correlate them with morphological changes. Our purpose then has been to determine the relation between the normal and abnormal ventricular complex and a morphologically normal or abnormal ventricular myocardium.

The general autopsy findings, the gross appearance of the pericardium and valves, the condition of the coronary vessels, the gross appearance of the heart muscle, and the microscopic appearance of sections from areas suspected of being abnormal were tabulated. Usually two or three sections were available for microscopic study from each heart, sometimes only one.

Pathological changes in the endocardium and aorta were not tabulated unless of evident clinical importance, as they were not considered capable of causing changes in the ventricular complex. The degree of coronary arteriosclerosis has been noted under the categories of slight, moderate, or marked. Although thrombosis of a branch may occur when the appearance of the remainder of the coronary tree is such as to indicate only moderate arteriosclerosis, yet such a case is noted as "marked" because of the degree of the change in the one branch which became thrombosed. When the term atheroma appeared in the original autopsy protocol it was carried over without change to our tables because it was thought best not to change the terminology of the recording pathologist. It is felt that atheroma of the coronaries is but one manifestation of arteriosclerosis of these vessels.

Morphological changes in the myocardium are especially stressed because it is felt that some such definite finding might account for permanent changes in the electrocardiogram. Lesions of the myocardium are considered separately from lesions of the coronary arteries because it is believed that the electrocardiogram can only be influenced by changes in the physiology of the myocardium. It is possible that coronary narrowing may so reduce the blood supply to the muscle fibers as to change the electrical curve without there being any morphological changes in the

fibers. It is impossible, however, to evaluate the degree of coronary narrowing with sufficient exactness to allow a correlation of this such as has been attempted here with morphological myocardial changes. It is also known that toxic influences and inflammation as in diphtheria and rheumatic fever may affect the muscle fibers so as to change the electrical curve. Sometimes toxic influences may produce morphological changes as well, but inflammation of course will always do so.

The ventricular myocardium, including under this term the muscular and fibrous tissue structure, was considered to show structural disease when the following morphological changes were found: (1) inflammatory changes: (a) exudative or proliferative lesions, be they localized or diffuse, such as are found in rheumatic or bacterial infections; (b) fibrosis resulting from acute or chronic inflammatory changes; (2) non-inflammatory changes, such as: (a) replacement fibrosis in areas of atrophied muscle fibers due to coronary narrowing, also scars following infarction due to coronary occlusion; (b) increase of intramuscular fibrous tissue; (c) fatty degeneration; (d) granular degeneration. It will be noted that these changes are demonstrable chiefly on microscopic examination.

Table 1 shows the relation of normal and abnormal ventricular complexes to normal or abnormal autopsy findings in the sixty cases studied.

TABLE 1.—RELATION OF VENTRICULAR COMPLEX AND AUTOPSY FINDINGS

	Ventricular Myocardium	
	Diseased	Normal
47 abnormal complexes	38 (81 per cent)	9 (19 per cent)
13 normal complexes	6 (46 per cent)	7 (54 per cent)

Of the 47 cases with abnormal ventricular complexes 81 per cent were found to have morphological changes in the ventricular myocardium and 19 per cent had apparently normal myocardium. Of the 13 cases with normal ventricular complexes 46 per cent were found to have morphological changes while 54 per cent had normal myocardiums. There was agreement between the electrocardiographic diagnosis and the autopsy findings in 45 cases, 75 per cent of the whole series, and disagreement in 25 per cent. The agreement was greater when the electrocardiogram was abnormal (81 per cent) than when it was normal (54 per cent).

With a normal electrocardiogram there appears to be about an equal chance for the myocardium to be found normal or diseased. This observation should lead us to be very cautious in interpreting a normal electrocardiogram as an indication of a normal myocardium. In doubtful cases we should take additional records or, if this is not possible, should rely for our diagnosis upon other clinical signs of myocardial disease, such as enlargement of the heart, abnormality of the heart sounds, or abnormal cardiac functional tests.

Of the seven cases with normal electrocardiograms and normal myocardium none had heart disease; one had slight coronary arteriosclerosis; one died of uremia and revealed fibrinous pericarditis with a heart weighing 550 gm.

Table 2 gives the morphological findings in the six cases with normal ventricular complex and an abnormality of the myocardium. These cases merit special attention because a negative diagnosis was made in the presence of myocardial disease. Only one of them had a clinical diagnosis of heart disease, Case 20. None died of heart failure. There were no gross focal lesions in any of these hearts nor any lesion of the muscle fibers. Changes in the interstitial tissue were slight in the first three

TABLE 2.—CASES WITH NORMAL VENTRICULAR COMPLEX—PATHOLOGIC CHANGES ON AUTOPSY.

Case No.	Age.	Cause of death.	Heart wgt., gm.	Gross appearance.	Microscopic findings in ventricles.
9	56	Bronchopneumonia; secondary anemia	425	Normal	Slight increase of interstitial fibrous tissue
17	51	Post-thyroidectomy (for Graves' disease), mediastinal hemorrhage and edema of larynx	350	Coronaries normal	Slight increase of fibrous tissue
19	65	Carcinoma of bile duct; bronchopneumonia	350	Muscle pale; coronaries normal	Few small areas of fibrosis
20	19	Acute septic endocarditis; mitral valve	300	Petechiae; coronaries normal	Polymorphonuclear foci in both ventricles, perivascular distribution, and scattered through interstitial tissue
21	59	Bronchopneumonia and pleurisy	235	Coronaries normal	Increased interstitial tissue especially in left ventricle
48	79	Bronchopneumonia	?	Subendocardial hemorrhages; coronaries—slight atheroma	Increased fibrous tissue in left ventricle

cases, moderate in the last three. The coronary arteries were normal in all but one case which showed slight coronary arteriosclerosis.

The nine cases of Table 3 showed an abnormal ventricular complex and a normal myocardium. These cases merit special attention because a positive diagnosis of myocardial disease was erroneously made on the basis of the abnormal features of their electrocardiograms. Five of them had a clinical diagnosis of heart disease (Cases 2, 4, 6, 7 and 14) three dying of cardiac insufficiency. Coronary arteriosclerosis was absent in three cases, slight in four, and moderate in two. Their electrocardiograms appear in Figs. 1, 2, and 3.

In seeking an explanation for the appearance of an abnormal electrocardiogram in these cases without myocardial degeneration or fibrosis, it may be noted that Case 7 had a very large heart and shows (Fig. 2C) the type of ventricular complex which has been attributed to marked

TABLE 3.—CASES WITH ABNORMAL VENTRICULAR COMPLEX. NO PATHOLOGIC CHANGES IN MYOCARDIUM.

Case No.	Electrocardiogram.		Cause of death.	Cardiac autopsy findings.
	QRS.	T.		
1 64	Deep Q-3; left axis	Normal	Cerebral hemorrhage	350 gm.; left ventricular hypertrophy slight; coronary arteries moderate arteriosclerosis; myocardium slight fatty infiltration
2 50	Normal axis; wide	T-2 diphasic six months before death; normal four days before death	Lobar pneumonia; coronary arteriosclerosis	390 gm.; hypertrophy slight; coronaries slight arteriosclerosis; myocardium normal
4 42	*Right bundle branch block		Heart failure; chronic valvular disease; mitral stenosis and insufficiency	460 gm.; left ventricle increased thickness; right ventricle dilated; coronary arteriosclerosis slight; myocardium normal
5 46	Normal axis; notched; high voltage low voltage		Bronchopneumonia, suppurative	370 gm.; myocardium normal; coronaries negative
6 26	Right axis; wide; notched	T-2 pseudoelectro	Heart failure, pulmonary embolism; chronic valvular disease; thrombotic mitral and tricuspid valve arthritis	500 gm.; left hypertrophied and dilated; coronaries negative; myocardium normal; muscle fibers increased in size on microscopic examination
7 49	Left axis; wide; notched; slurred	T-1 and T-2 negative; R T-1 depressed; R T-2 elevated	Ruptured aneurysm of aorta	500 gm.; left ventricle hypertrophy marked; aortic insufficiency; coronaries slight arteriosclerosis; myocardium normal
11 53	Right bundle branch block		Heart failure, pulmonary embolism	400 gm.; right ventricle hypertrophied and dilated; left ventricle hypertrophied; coronaries normal; myocardium normal
22 39	Left axis; low voltage	Normal	Syphilis of heart	250 gm.; coronary arteriosclerosis moderate; myocardium normal
27 38	Left axis; negative	Low voltage	Lobar pneumonia	350 gm.; coronaries slight arteriosclerosis; right coronary artery slightly narrowed; inactive aortitis; aortic insufficiency; left ventricular cavity enlarged; myocardium normal

* Atrial fibrillation.

† Partial heart block.

hypertrophy of the left ventricle.¹ However, Case 27 with aortic insufficiency and a heart much larger than that of Case 7, did not show this special type of ventricular complex (Fig. 3C) so that its association with left ventricular hypertrophy is clearly not obligatory. The low voltage

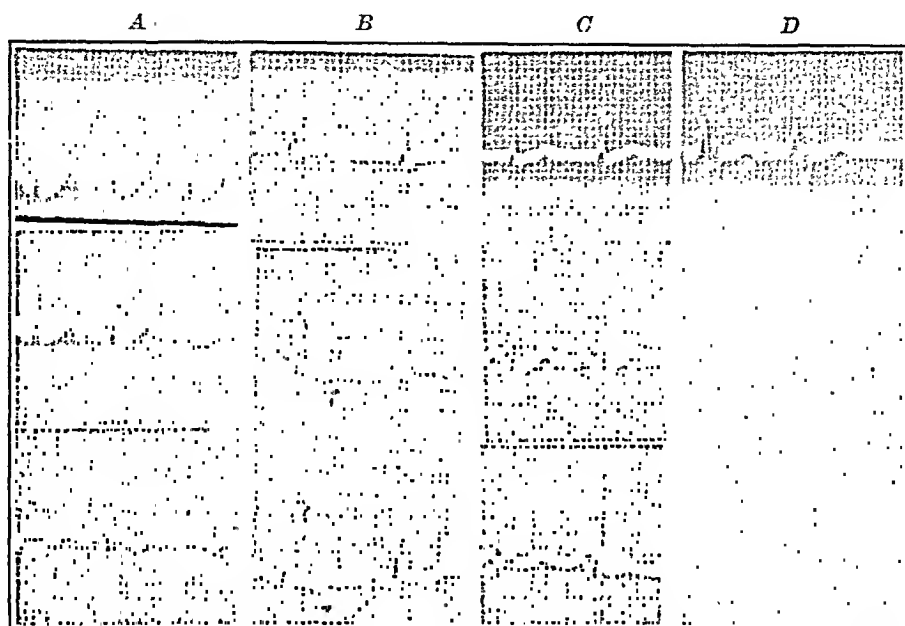


Fig. 1.—A. Case 1. B. Case 2, six months before death. C. Case 2, five days before death. D. Case 4.

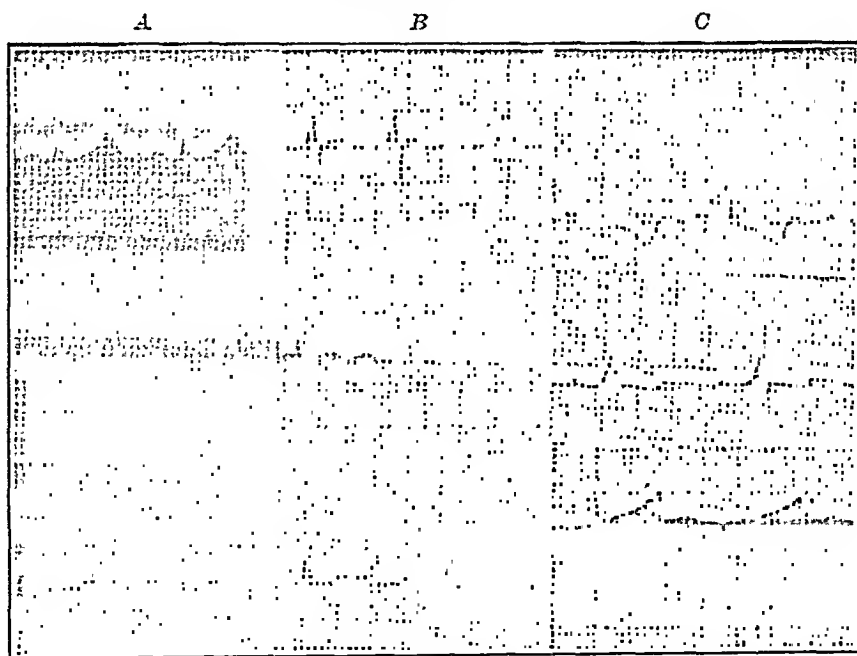


Fig. 2.—A. Case 5. B. Case 6. C. Case 7.

T-wave of Case 27 might be explained as a result of the toxemia of the pneumonia, but the high voltage T of Case 5, also with pneumonia, appears to clash with this idea. The abnormal Q_s of Case 1 might be due to the occurrence of moderate coronary arteriosclerosis and slight fatty infiltration of the myocardium in an adipose individual with a transverse position of the heart.

Case 2 had previously been admitted for an attack thought to be a minor coronary closure, at which time the T-wave was diphasic in Lead II (Fig. 1*B*). The record just before death was normal (Fig. 1*C*). Slight coronary arteriosclerosis and slight hypertrophy were the sole morphological findings. It is possible that the earlier T-wave changes were on a basis of functional muscle disturbance, due to coronary narrowing and a deficient blood flow which had not yet resulted in morphological changes in the muscle fibers or interstitial tissue. It is impossible to deny however that more extensive section cutting might have discovered areas of morphological change.

In Case 22 the hepatic toxemia might explain the low voltage QRS group. No explanation seems possible for the low voltage, notched QRS

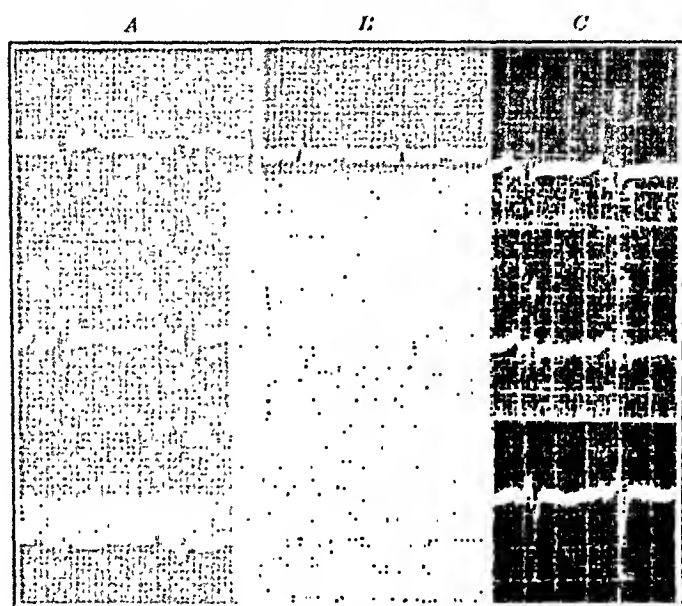


Fig. 3.—A. Case 14. B. Case 22. C. Case 27.

with large T of Case 5 or for the wide notched QRS with isoelectric T₂ of Case 6. One can only fall back on the rather weak plea that more extensive microscopic sections from these hearts might have discovered localized changes in morphology. This, however, does seem to be a likely explanation of the failure to find structural changes in Cases 4 and 14 with typical right bundle-branch block² for we know that a small lesion in the septum affecting the bundle branch tissue might cause this and a detailed sectioning of the bundle area would be needed to find a small lesion.

Table 4 gives the details of the 38 cases with abnormal ventricular complex and with morphological changes in the myocardium. These have been roughly grouped according to whether the myocardial changes were slight or marked or intermediate. There are ten with slight changes, 3 of these with a clinical diagnosis of heart disease, 14 with moderate

changes, with six cases of clinical heart disease, and 14 with marked changes, 10 with clinical heart disease.

Reviewing the electrocardiographic features of the 53 cases of Tables 2, 3, and 4, one fails to find a close relationship between the degree of the pathological changes and the character of the electrocardiographic abnormality. For example, Case 21 of Table 2 had increased interstitial tissue especially in the left ventricle, and gave a normal electrocardiogram, while Case 24 of Table 4 which had slight fibrosis throughout both ventricles and Case 18 of Table 4, which had acute purulent myocarditis with edema and polymorphonuclear cells in the stroma, had an electrocardiogram with notching and slurring of the QRS group. Case 24 had less evidence of disease than Case 21 whose electrocardiogram was normal. Case 18 had more evidence of disease than Case 24, yet the electrocardiographic changes were the same. Note also Cases 26 and 43 of Table 4, each of which had an inverted T_1 of the coronary type. Case 26 showed a mild fibrosis of the myocardium with a few areas of lymphocytic infiltration and few areas of slight edema. Case 43 showed cicatricial scars of the myocardium, roughened pericardium and, on microscopic examination, marked fibrosis. Moreover, Case 30 with only small areas of fibrosis in the myocardium, showed the electrocardiogram of left bundle-branch block.

There were, however, some noteworthy associations of electrocardiographic features with pathological pictures. There were ten cases with marked coronary and acute degenerative myocardial changes. Six of these (Cases 25, 33, 44, 45, 47, and 50) gave electrocardiograms with abnormal elevation or depression of the S-T interval. Infarcts were not always found in these hearts but it is possible that in those without infarcts the marked degenerative myocardial lesions present would affect the electrical curve as does an infarct. Of the four other cases with degenerative myocardial changes (Cases 35, 40, 54, and 61) one gave the electrocardiogram of right bundle-branch block (Case 40) and the other three showed the coronary T-wave commonly associated with a healing coronary lesion. It is of interest to find that all ten hearts with marked myocardial changes due to coronary arteriosclerosis were associated with abnormal electrocardiograms, and all except the one with bundle-branch block showed the T-wave changes commonly recognized as associated with some phase of acute myocardial degeneration.

Of the 5 cases with a T-wave of the coronary type, three (35, 54, and 61, Table 4) showed coronary thrombosis or areas of necrotic myocardium. One case (43, Table 4) showed a roughening of the pericardium with fibrin formation which might have been the cause of the T-wave peculiarity,⁵ while the other patient (26, Table 4), who died of uremia, failed to show any focal lesion and only slight coronary and myocardial changes. The predominance of focal myocardial lesions

TABLE 4.—CASES WITH ABNORMAL VENTRICULAR COMPLEX AND MYOCARDIAL DISEASE.

Case No.	Electrocardiogram.		Cause of death.	Gross appearance.	Microscopic of myocardium.
	QRS.	T.			
15	L. axis	T-1 inv.	Arteriosclerotic heart disease with failure	(Slight) 680 gm. enlarged; pericardium normal; coronaries show patches of atheroma	changes) Some increase in size of fibers. Increase of interstitial fibrous tissue throughout
24	L. axis; notched and slurred	Normal	Lobar pneumonia	450 gm. myocardium neg.; pericardium inflamed surface; no fluid; coronaries tortuous with patches of atheroma	Slight fibrosis throughout both ventricles
26	Axis normal; QRS neg.	T-1 inv.; coronary type	Uremia	Not enlarged; myocardium neg.; pericardium normal; coronaries show slight atheroma	Mild fibrosis; few areas of leukocytic infiltration; few areas slight edema
29	Axis normal; low voltage	T-2 diphasic; low voltage	Lobar pneumonia	380 gm. myocardium normal; pericardium normal; coronaries slight atheroma	No fibrosis; few areas with lymphocytes and plasma cell infiltration
30	Left bundle branch block		Carcinoma of stomach	340 gm. myocardium normal; pericardium normal; coronaries normal	Small areas of fibrosis
32	Axis normal; low voltage	Low voltage	Purulent bronchopneumonia	Myocardium normal; pericardium normal; coronaries normal	Granular degeneration
42	L. axis; notched and slurred	Normal	Bronchopneumonia	300 gm. myocardium shows greyish areas; pericardium normal; coronaries atheromatous	Some fibrosis
51	*L. axis; low voltage	T-1 and T-2 inv.	Mitral stenosis; cardiac failure	445 gm. hypertrophy of right ventricle; pale fibrotic patches in myocardium; pericardium normal; coronaries neg.	Slight fibrosis left ventricle
56	*L. axis	T-1 and T-2 inv.	Mitral stenosis; heart failure	625 gm. dilated and hypertrophied; pericardium neg.; coronaries some atheroma; no narrowing	Very slight fibrosis
57	L. axis; wide; notched and slurred	T-1 inv.	Acute cholecystitis	275 gm. myocardium normal; pericardium neg.; coronaries few small atheromatous patches	Slight amount of fibrosis
3	L. axis	Low voltage	Mediastinal tumor; empyema	(Moderate) Heart involved in tumorous mass. Pericardial adhesions; coronaries normal	changes) Slight increase in interstitial tissue
8	L. axis; low voltage; notched and slurred	T-1 iso-electric	Lobar pneumonia	800 gm. much enlarged; pericardium normal; coronaries normal	Extreme fibrosis
13	tL. axis; wide; notched and slurred	Normal	Arteriosclerotic heart disease; heart failure	760 gm. enlarged; myocardium pale; pericardium normal; coronaries—thickened walls; right coronary orifice 1 mm. in diameter	Many large muscle fibers; scattered patches of fibrosis

18	29	R. axis; notched and slurred	Normal	Mitral stenosis and insufficiency; acute endocarditis; heart failure	Heart enlarged; myocardium pale; pericardium normal; coronaries normal	Acute purulent myocarditis; edema; polys in stroma
23	72	L. axis	T-2 iso-electric	Subacute bacterial endocarditis	450 gm. myocardium neg.; pericardium complete fibrous adhesions; small amount of slightly cloudy fluid; coronaries atheromatous	Fragmentation of muscle fibers; slight fibrous infiltration beneath pericardium
28	45	L. axis	Low voltage	Cerebral hemorrhage	510 gm. hypertrophied; dilated; pericardium normal; coronaries moderate atheroma	Moderate fibrosis both ventricles with small areas where muscle bundles are separated by bands of loosely organized fibrous tissue
39	17	R. axis; notched and slurred	Normal	Mitral stenosis and aortic insufficiency; heart failure	425 gm. enlarged; myocardium and pericardium neg.; coronaries neg.	Small areas subpericardial fatty degeneration. Slight increase perivascular fibrous tissue; few foci, leukocytes and monocytes; occasional small areas intramuscular fibrous tissue
41	70	L. axis; wide	T-1 inv.	General arteriosclerosis; myocardial fibrosis; heart failure	400 gm. scarred left ventricular wall; pericardium neg.; coronaries calcified and narrowed	Scattered large fibrous scars
49	55	L. axis; wide	T-1 inv.	Aortic stenosis; paroxysmal tachycardia; heart failure	550 gm. hypertrophied; dilated; few pale, fibrous patches; pericardium normal; coronaries few patches atheroma	Hypertrophied muscle fibers; patches of fibrosis
52	45	L. axis; wide; notched and slurred	Normal	Bronchopneumonia	750 gm. hypertrophy; dilated; areas of fibrosis; suppurative pericarditis; coronary sclerosis	Increase of fibrous tissue; polys and mononuclear infiltration
53	12	Axis normal; low voltage	T-2 inv.	Streptococcus septicemia	225 gm. dilated; grayish-white areas; pericardial normal; coronaries normal	Vessels show intimal proliferation; some vessels occluded; acute myocardial degeneration
54	55	L. axis; wide	T-1 inv.; coronary type	Pulmonary abscess; actinomycosis	525 gm. dilated; hypertrophied; pericardium normal; coronaries show marked atheroma; clot in lumen of left descending coronary	Few fibrotic areas
55	78	L. axis; wide; notched and slurred	T-1 and 2 inv.	Pericardial abscess	400 gm. grayish areas in myocardium; pericardium fibrous adhesion between visceral and parietal layers; coronary sclerosis	Fibrosis and hypertrophy of muscle fibers
60	82	*Right bundle branch block		Bronchopneumonia	850 gm. dilated; hypertrophied; areas of fibrosis; pericardium normal; coronaries sclerotic	Considerable scattered patchy fibrosis
61	55	Normal axis	T-1 and 2 inv.; coronary type	Uremia	550 gm. dilated; hypertrophied; fibrosis involving posterior papillary muscle; coronaries sclerotic; pericardium neg.	<i>changes</i> Areas of focal necrosis and cellular infiltration; areas of fibrous replacement
65	63	Axis normal	T-2, T-3 diphasic; ST-2 elevated	Coronary thrombosis	575 gm. myocardium left ventricle, apex thin and shows grey streaks; pericardium small, amount slightly cloudy fluid; coronaries atheromatous; thrombosis right coronary	Fibrosis; leukocytic infiltration, fibrous tissue apex left ventricle

* Auricular fibrillation.

† Partial heart block.

TABLE 4.—CASES WITH ABNORMAL VENTRICULAR COMPLEX AND MYOCARDIAL DISEASE.—(Continued.)

Case No.	Age	Electrocardiogram.		Cause of death.	Gross appearance.	Microscopic of myocardium.
		QRS.	T.			
33	40	L. axis; wide; notched and slurred	T-1 iso-electric; low voltage; ST-1 elevated	Myocardial infarct	(Marked) 720 gm. lower part left ventricle thin and fibrosed; pericardial surface retracted; coronaries thickened and narrowed; occlusion lower part of anterior descending branch left coronary	Changes—(Cont.) Areas of necrosis of muscle cells with fibroblasts and leukocytes
34	42	L. axis; wide	T-1 and T-2 inv.	Arteriosclerotic heart disease; heart failure	525 gm. myocardium neg.; subpericardial hemorrhage anterior surface; coronaries sclerotic and calcified	Fibrosis marked in left ventricle
35	50	L. axis; large Q-3	T-1 and T-2 inv.; coronary T-2	Myocardial infarct	430 gm. dilated; apex of left ventricle infarcted; pericardium neg.; coronaries calcified and narrowed	Fibrosis with area of necrosis
36	63	*Axis normal; wide	T-1 iso-electric; T-2 neg.	Miliary tuberculosis of the lung; myocardial fibrosis; cardiac insufficiency	600 gm. myocardium thickened, pale and scarred. Pericardium 100 cc. fluid; coronaries sclerosed and tortuous	Marked diffuse fibrosis
38	76	L. axis	T-1 inv.; low voltage	Volvulus	425 gm. fibrotic areas at apex. Pericardial adhesions and hydropneumothorax; coronaries marked calcification; left circumflex obliterated	Extreme fibrosis
40	53	Right bundle branch block		Coronary arteriosclerosis; heart failure	525 gm. myocardium shows small greyish areas; pericardium neg.; coronaries show atheroma with marked narrowing descending branch of left coronary	Subendocardial round cell infiltration; necrotic muscle cells, areas of fibrosis
43	55	L. axis	T-1 inv.; coronary type	Uremia	425 gm. myocardium shows cleaveland scars; pericardium roughened surfaces; layer of fibrin; slight increase of fluid; coronaries atheromatous and calcified	Marked fibrosis
44	52	Right bundle branch block coronary T-1 and T-2		Myocardial infarct	305 gm. hypertrophy and dilatation; infarct anterior wall left ventricle; pericardial adhesions; coronary sclerosis marked; thrombosis anterior descending branch left coronary	Marked fibrosis, area of muscle necrosis
45	82	Left bundle branch block ST-1 inv.; ST-2 and 3 upward		Arteriosclerotic heart disease; coronary occlusion	530 gm. old infarct at apex; several fibrotic areas; pericardium normal; coronaries sclerotic; much narrowed	Marked fibrosis, pale muscle fibers
46	48	Axis normal; wide; notched and slurred; large Q-3	T-1 iso-electric; low voltage	Septicemia; bronchopneumonia	325 gm. many areas of fibrosis; pericardium normal; coronaries sclerotic, narrowed	Fibrosis both ventricles
47	69	Axis normal; QRS low voltage	T-1 inv.; ST-1 upward; ST-3 inv.	Coronary thrombosis	Enlarged; greyish areas at apex; pericardium normal; coronary sclerosis marked; clot in left coronary	Considerable interstitial fibrosis
50	15	R. axis	T-1 inv.; ST-2 and ST-3 elevated	Coronary thrombosis	575 gm. dense fibrosis in left ventricle posteriorly; hemorrhagic area posterior margin right ventricle; pericardial adhesions apex left ventricle; increased fluid; occlusion posterior and anterior descending branches left coronary	Old fibrosis; area infarction

* Auricular fibrillation.

† Partial heart block.

in these five cases is an important confirmation of the frequent association of this coronary T-wave with the less acute phases of focal myocardial lesions due to coronary narrowing or occlusion. The other two cases serve to emphasize the fact previously demonstrated, that this is not a constant association and may be the result of a different type of myocardial disease.

It is difficult to consider the anatomical basis of the individual abnormal features of the electrocardiogram because these rarely occurred alone in this series. Certain cases, however, showed only a single abnormality of the curve. The one case whose record showed a large Q_s as the sole abnormality (Case 1, Table 3), was found to have a transverse heart, moderate coronary arteriosclerosis, slight fatty infiltration of the myocardium but no degeneration or fibrous changes. There were six cases whose records showed a QRS group significantly notched and slurred with normal T-waves. None of these had a normal myocardium. Two showed slight and four, moderate, diffuse myocardial changes. Two with right axis deviation of QRS (18 and 39, Table 4), had mitral stenosis and moderate diffuse myocardial changes. Two with left axis deviation (24 and 42, Table 4) had atheromatous coronaries and slight diffuse myocardial fibrosis. Two others with left axis deviation (13 and 52, Table 4), and with an increased duration of QRS as well as notching, showed very large hearts (750 gm.), coronary arteriosclerosis and moderate diffuse myocardial changes. That these two very large hearts were the only ones of the six with notched QRS to show abnormal duration as well, is in favor of Lewis' suggestion that abnormal duration of QRS may be due to a considerable increase in thickness of the left ventricular muscle³ and against Wilson's contention that abnormal duration is usually due to an intraventricular conduction defect.⁴

A further study of the relation of heart size and QRS duration in this series fails to give unqualified support to either theory of its causation. Considering the QRS duration in all records with left axis deviation, excluding those diagnosed as bundle-branch block, it is found that the average heart weight of the 15 with a normal duration was 485 gm. while the average heart weight of the 11 with increased duration was 560 gm. This suggests a direct relation between heart size and QRS duration but there are two very large hearts (case 15, 680 gm., and case 8, 800 gm.) with a normal duration of QRS and one very small one (case 57, 275 gm.) with increased duration. Heart size evidently need not cause QRS prolongation and cannot be its sole cause. One must, of course, consider the possibility of a disproportionate thickening of the left ventricle which might prolong the spreading of the contraction more than it would contribute to an increase in heart size.

Low voltage of QRS was the sole abnormal feature of the curve in one case (22, Table 3) dying of liver toxemia, and in one other case (5, Table 3) it was complicated by a high voltage T-wave in a patient with bronchopneumonia. Neither of these hearts showed morphological myocardial changes, though in the first one there was moderate coronary arteriosclerosis. In all eight hearts with only QRS changes in the electrocardiogram the myocardial changes were negative, slight, or moderate. No instance of marked changes occurred.

When the T-wave was inverted, isoelectric or diphasic in Lead I (7 cases), in Leads II and III alone (6 cases), or in Leads I and II together (10 cases), there was usually some other abnormal feature in the curve. In each of these groups the degree and the character of the pathological changes were so varied that it would be impossible to say that there was a predominant association.

The bundle-branch block cases are interesting as to the varied extent of the pathological changes discovered, for it is found that of five with right bundle-branch block two did not reveal any morphological myocardial changes except hypertrophy, one showed moderate changes, and two marked changes. Of the two cases with left bundle-branch block, one showed slight changes and one marked.

There were only six cases of rheumatic valvular disease. One of these had a normal electrocardiogram (Case 20, Table 2), and one with right bundle-branch block had a negative myocardium (Case 4, Table 3, and Fig. 1). The other four had varied myocardial and electrocardiographic abnormalities.

There were only six cases with slight coronary arteriosclerosis uncomplicated by any other condition which might have affected the electrocardiogram. Two of these had a normal myocardium and normal electrocardiogram though one had shown a diphasic T_2 six months before death (Case 2, Table 3, and Fig. 1). One had a normal electrocardiogram with slight increase of fibrous tissue in the left ventricle (Case 48, Table 2). The other three showed various types of myocardial and electrocardiographic abnormality. These cases are too few of either rheumatic or slight coronary arteriosclerotic disease to allow any conclusion to be drawn except that either may exist with or without myocardial changes and with or without electrocardiographic abnormality. In either etiological group those cases with definite myocardial changes are much more likely to have electrocardiographic abnormality than are those with normal myocardium.

Three patients died of uremia, 26, 61, and 43. They showed various degrees of coronary arteriosclerosis and myocardial disease, and case 26 only slight changes. It is significant that all three showed T_1 inversion with the "coronary type" of curve. This association has been also noted by others.

A review of the literature revealed but few comparable observations. Either the electrocardiographic criteria were not clearly stated or the autopsy reports did not include a statement of microscopic findings, or only cases with abnormal electrocardiograms had been considered.

Nathanson⁶ published 7 suitable case reports (his series numbers 1, 2, 3, 5, 6, 7, 9), but only reported upon cases showing an abnormal electrocardiogram. In each heart he found marked coronary and myocardial disease.

Willius and Brown⁷ published 20 suitable case reports (cases 2, 3, 5-8, 10, 11, 12, 14-19, 21-25) 9 with normal and 11 with abnormal inversion of T (T_1 or T_2). They did not consider any other abnormality of the ventricular waves, except T-wave inversion. Four cases showed normal T-waves and normal muscle, 9 showed abnormal T-waves and abnormal muscle, 5 showed normal T-waves and abnormal muscle, 2 showed abnormal T-waves and normal muscle. This represents agreement in 65 per cent, disagreement in 35 per cent, very like the agreement in 75 per cent and disagreement in 25 per cent of the present group.

Saphir, Priest, Hamburger, and Katz⁸ studied a series of cases found at autopsy to have "advanced coronary arteriosclerosis"; 19 of these had suitable autopsy reports and electrocardiograms and all showed abnormal records and definite myocardial changes.

Rykert and Hepburn¹ studied 20 cases showing a special type of abnormality of the electrocardiogram seen in Fig. 2C which they believed due to marked left ventricular preponderance or hypertrophy. All but four of their cases showed definite morphological myocardial changes of various types but these four showed only hypertrophy of the individual muscle fibers.

The only series of cases really comparable with the present one are those of Markel and Pardee⁹ with 10 cases and Master and Pardee¹⁰ with 11 cases, two of which are unsatisfactory because of digitalis administration having affected the T-waves. The 19 suitable cases of these two series were studied in much the same manner as the present group and included 3 with normal electrocardiograms and normal myocardium, 16 with abnormal electrocardiograms and abnormal myocardium, there being no such lack of agreement as was found in the cases of Tables 2 and 3 of the present group. These 19 cases showed on the average more marked pathological changes than the present series, probably because they were selected solely from the medical wards and did not include some of the less important cardiac lesions found in the present group selected from the autopsy service of the entire hospital.

DISCUSSION

From these observations it seems that the only electrocardiographic abnormality which we can constantly associate with severe morphological

changes is an abnormal deviation of the S-T interval. Further, when the T-wave is not inverted, even though there be abnormalities of the QRS group or a low voltage of T, we should expect to find mild rather than severe lesions.

Case 7, Table 3, and four cases reported by Rykert and Hepburn, suggest that marked left ventricular hypertrophy without other morphological changes may at times cause a characteristic deformity of QRS, and T and the S-T interval.

The finding of a normal record does not exclude the presence of slight or moderate interstitial fibrosis or a subacute inflammatory reaction in the interstitial tissue, for such things were found in the cases of Table 2. On the other hand, an abnormal record, even of right bundle-branch block does not with certainty indicate the presence of coronary disease or of morphological myocardial changes of any considerable extent. Slight coronary arteriosclerosis was sometimes associated with an abnormal electrocardiogram, more usually so when there were also morphological myocardial changes. Coronary arteriosclerosis, if more than slight, was always associated with an abnormal electrocardiogram. Rheumatic valvular disease was also more likely to be found associated with an abnormal electrocardiogram when myocardial changes were present.

The closest relation between the myocardial changes and the electrocardiogram was found in the group with marked coronary disease. All of these hearts gave electrocardiograms with definite abnormalities and when there were large areas of degenerated myocardium the T-wave changes commonly associated with coronary disease were always present—either the R-T deviation associated with infarction or the coronary T-wave associated with a healed or healing lesion.

The lack of correlation between the morphological myocardial changes and the electrical curve is explainable on several grounds. Since the electrical curve is produced by the action of the muscle fibers, a deficient coronary flow may conceivably cause changes in function without for a time, changes in structure taking place (Case 2, Table III, and Fig. 1, B and C). Moreover, it seems possible that similar functional changes in the muscle may arise with different structural backgrounds. This is apparent in the cases of Tables III and IV, where similar ventricular complexes are seen to arise with a quite different myocardial picture. Some of the instances of failure to find myocardial changes (Table III) may be due to the limited amount of the myocardium examined microscopically. This is especially so in the cases with right bundle-branch block, for here a relatively small lesion involving the bundle branch would not attract attention on gross inspection, and sections of the affected area would not be made.

It is felt that further progress in correlation of electrocardiograms and autopsy findings will only be possible when the myocardium is examined

in more numerous areas and particularly in relation to the position of the heart in the chest. Many of the anatomical descriptions in these autopsy protocols referred to the heart in such a way that it was not possible to decide whether the lesion was on the anterior or diaphragmatic or posterior or lateral walls of the heart. This geographical distribution of lesions is very important in its bearing on electrocardiographic diagnosis and therefore warrants much more attention than it has previously received.

SUMMARY

Sixty cases have been studied in attempting to determine a relation between the character of the ventricular complex of the electrocardiogram and the pathological findings in the ventricular myocardium.

Of 13 cases with a normal ventricular complex, a normal myocardium was found in 7. In the other six there were slight morphological changes.

Of 47 cases with abnormal ventricular complexes a normal myocardium was found in 9 (19 per cent). The abnormal features of the electrocardiograms in these 9 cases were similar to those found in other cases which revealed slight or moderate pathological changes in the myocardium. In the other 81 per cent of cases with abnormal ventricular complexes there were definite myocardial changes. When the electrocardiographic abnormality involved only the QRS group, the T-wave being normal, there were found only slight or moderate myocardial changes.

Although there was, in general, an association of increased duration of QRS with cardiac enlargement, yet there were notable exceptions.

When the T-wave was abnormal, with or without QRS abnormality, there was a great range in the extent and the degree of the myocardial changes discovered. A frequent but not constant association was seen between the coronary T-wave and focal myocardial lesions. There was a constant association between an elevated or depressed S-T interval and the finding of areas of acute myocardial degeneration, though not always with areas of infarction. The ventricular complex attributed to marked left ventricular hypertrophy affords an exception to this statement regarding the S-T interval.

Right bundle-branch block occurred twice without morphological myocardial changes being discovered and three times with such changes. Left bundle-branch block occurred twice, each time associated with myocardial changes.

A review of the literature showed a few comparable studies, all of which were in general agreement with these findings.

The authors wish to acknowledge their indebtedness to Dr. Robert A. Moore for help in reviewing many of the microscopic sections.

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OBSERVATIONS ON THE CARDIO-ACCELERATOR REFLEX FROM STIMULATION OF THE SKIN TEMPERATURE RECEPTORS*†

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I. THE INFLUENCE OF AGE UPON THE EFFECT OF SKIN TEMPERATURE STIMULATION ON THE HEART RATE

AS INDICATED in our previous report,² the heart rate appears to be influenced to a much greater degree by the skin temperature than by the body temperature itself. That is, by lowering or raising merely the skin temperature, the heart rate may be decreased or increased, quite independently of any changes in the body temperature.

Further studies now seem to indicate that the efficiency of this reflex action between the skin sense organs and the heart rate tends to vary inversely as the age of the individual. That is, the sensitivity—the degree and promptness—with which the heart reacts to the skin temperature changes, becomes less pronounced with age. We have aimed to illustrate this modifying influence of age in Charts 1 to 6.

The media employed in changing the skin temperature were water, air, and radiant heat. For the water applications we used a Crane continuous flow tub in which the inlet is constructed to mix the incoming flow so thoroughly as to insure a temperature uniformity of within one degree throughout the tub. The assurance of such uniform temperature throughout the tub is of high importance in such tests as these discussed here, since we have found that variations in skin temperature over such a fractional body area as the foot and lower leg, exercise a definite influence upon the heart rate.

Fig. 1 shows our set-up as used with the water bath. As mentioned in our previous report² we obtained by this method a continuous mechanical recording of the bath (skin) and body temperatures as well as the pulse (heart) rate.

For the hot air-radiant heat applications, we used a Burdick horizontal type cabinet, slightly modified for our experiments. The temperature changes and the heart rate were obtained by the same mechanical

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The following companies furnished most of the apparatus necessary:
Consolidated Ashcroft Hancock Co., Inc.; The Brown Instrument Company; The Burdick Corporation; The Crane Company; The Powers Regulator Company.

methods as described above for the water bath, except that the air temperature of the cabinet was read by means of a mercury thermometer placed about six or eight inches from the body. The initial temperature of the cabinet was about 80° F. for each experiment, and the thermometer was read at five-minute intervals, or oftener, throughout the experiment.

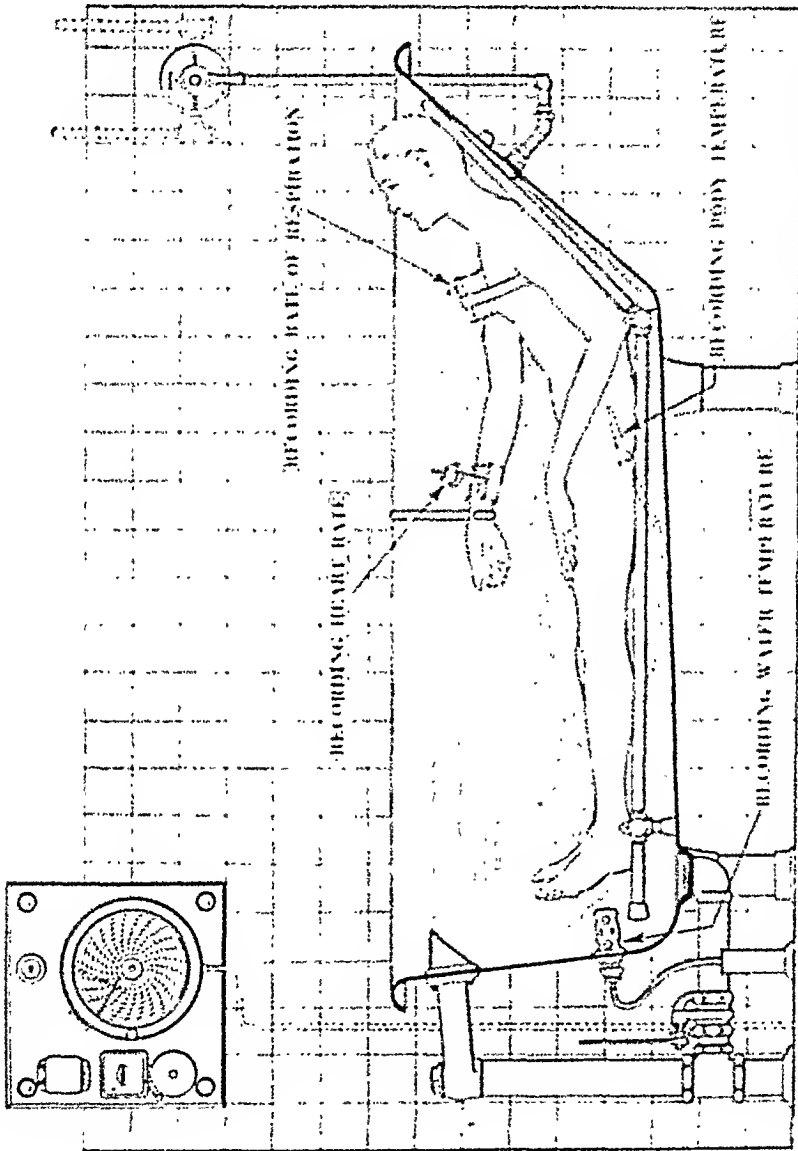


Fig. 1.—Scientific equipment and methods used with water in the determination of the relative influence of external and body temperature upon the heart. (By courtesy of the Crane Company, Chicago, Ill.)

In view of the relationships indicated in this paper between the bath (skin) temperatures and the heart rate, it should be emphasized here that while the temperature of the water is transmitted uniformly to all parts of the skin submerged, the temperature of the hot air and the radiant energy are not transmitted with equal uniformity to all parts of the skin enclosed in the cabinet. The reason being, of course, that the part of the body (usually the back) resting on the floor of the horizontal cabinet cannot be directly affected by the radiant heat emitted from the

top and sides of the cabinet, nor very effectively so by the hot air itself. This fact, no doubt serves to explain in part, the difference in effects upon the heart by the water bath and the radiant heat-hot air bath.

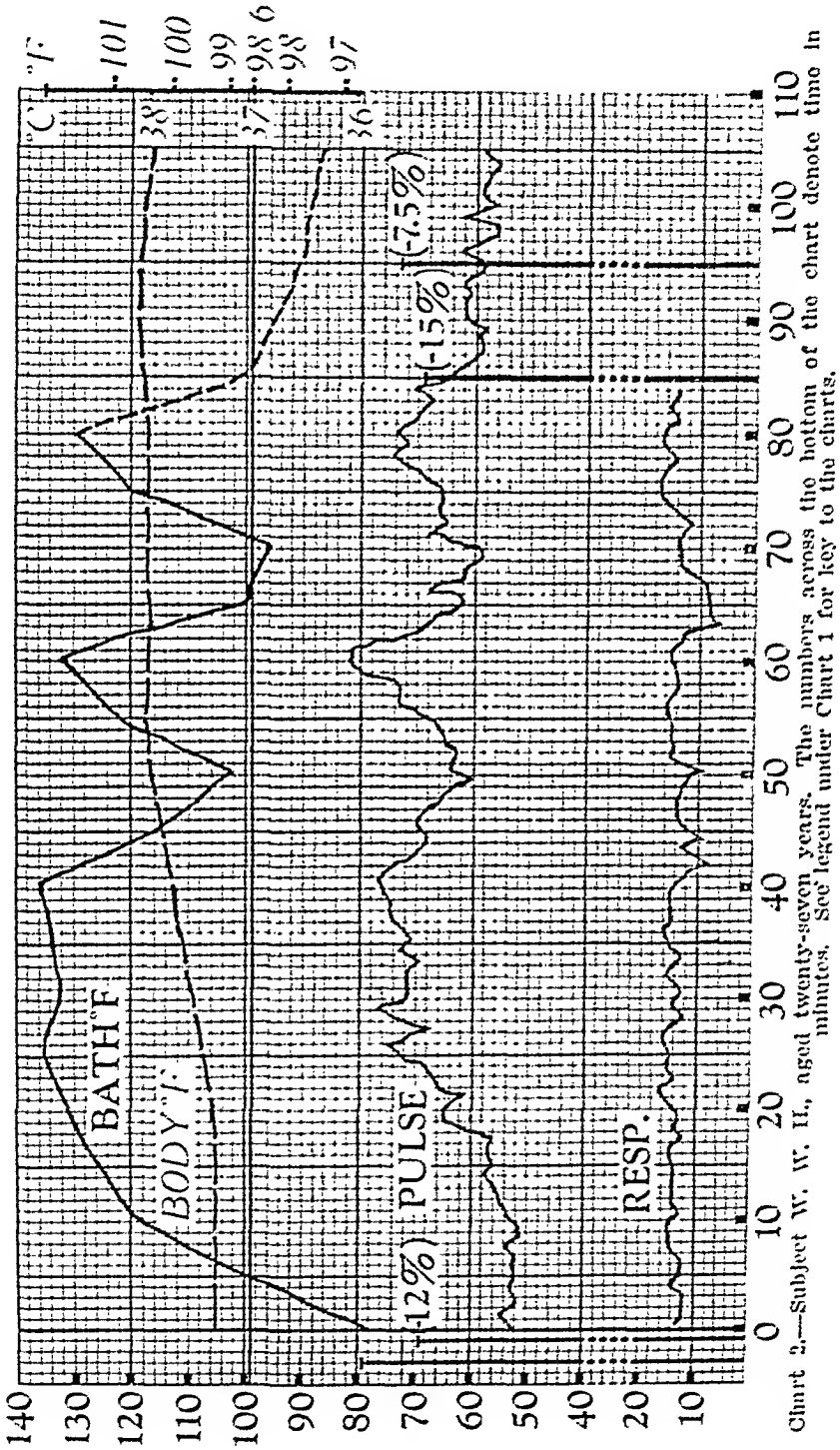
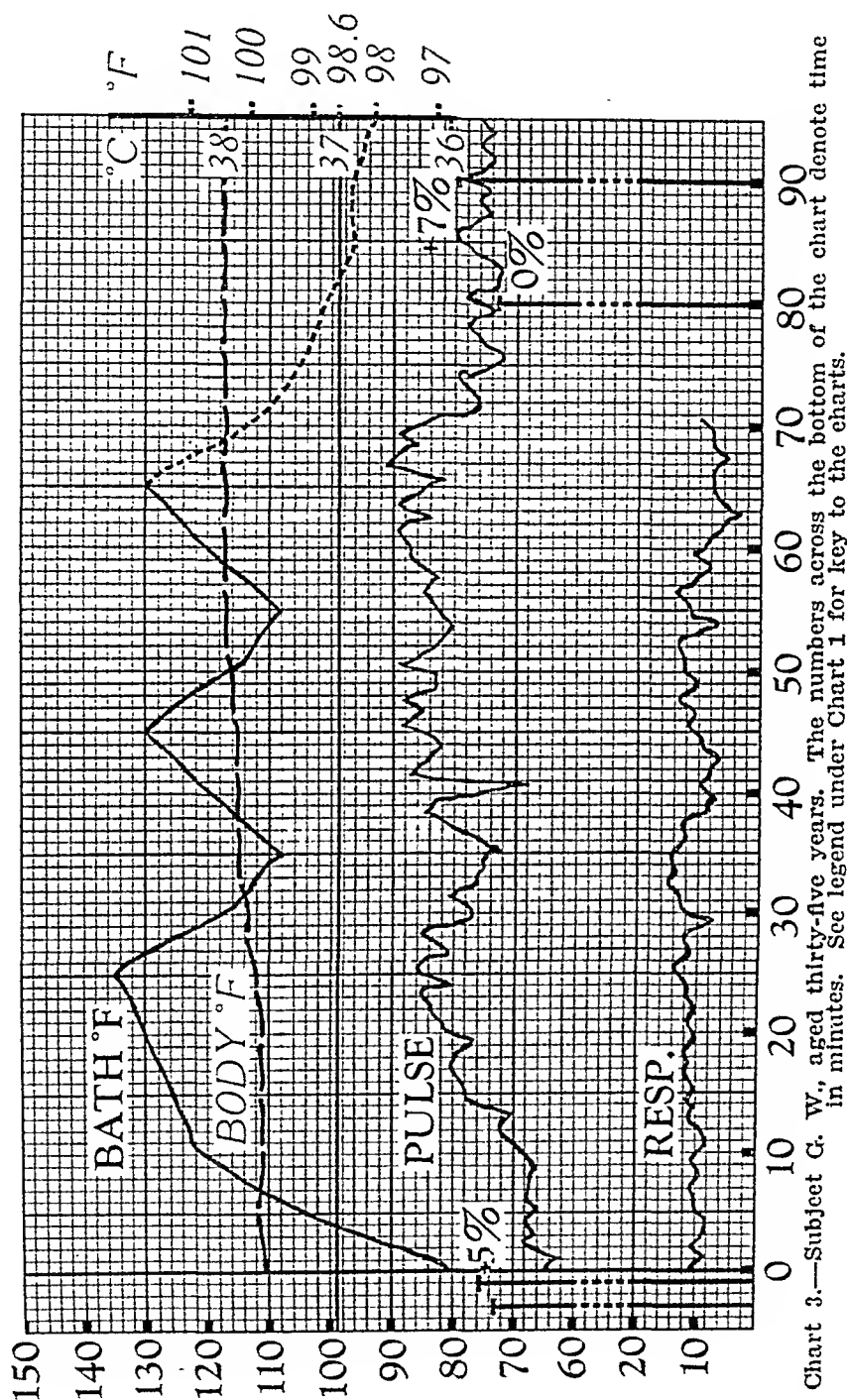


Chart 2.—Subject W. W. H., aged twenty-seven years. The numbers across the bottom of the chart denote time in minutes. See legend under Chart 1 for key to the charts.

The relationships indicated below, were obtained by dividing the change in heart rate, CHR, by the change in bath temperature, CBT, observed during some chosen time period. (The bath temperature is

considered equivalent to the skin surface temperature.) In Chart 1, then, if the increase in heart rate, CHR, during the first twenty-five minutes be divided by the rise in bath temperature, CBT, during the same period, we obtain the following relationship: $\text{CHR}/\text{CBT} = 51/62$



= 0.82. That is, as the bath temperature rises one degree Fahrenheit, the heart rate increases 0.82 of one beat.

A similar relationship is also obtained when the bath temperature is lowered: From the 65th to the 75th minute, Chart 1, there is a drop of 26 degrees in the bath (skin surface) temperature, and the heart rate decreases 28 beats. The ratio of CHR/CBT in this case becomes

$28/26 = 1.07$. This is somewhat higher than the 0.82 obtained above, and the average of the two figures, 0.82 plus 1.07, namely 0.95 is probably the more correct value here. Hence, in the case of this twenty-year-old individual, when he is subjected to a dry air-radiant heat bath, his heart

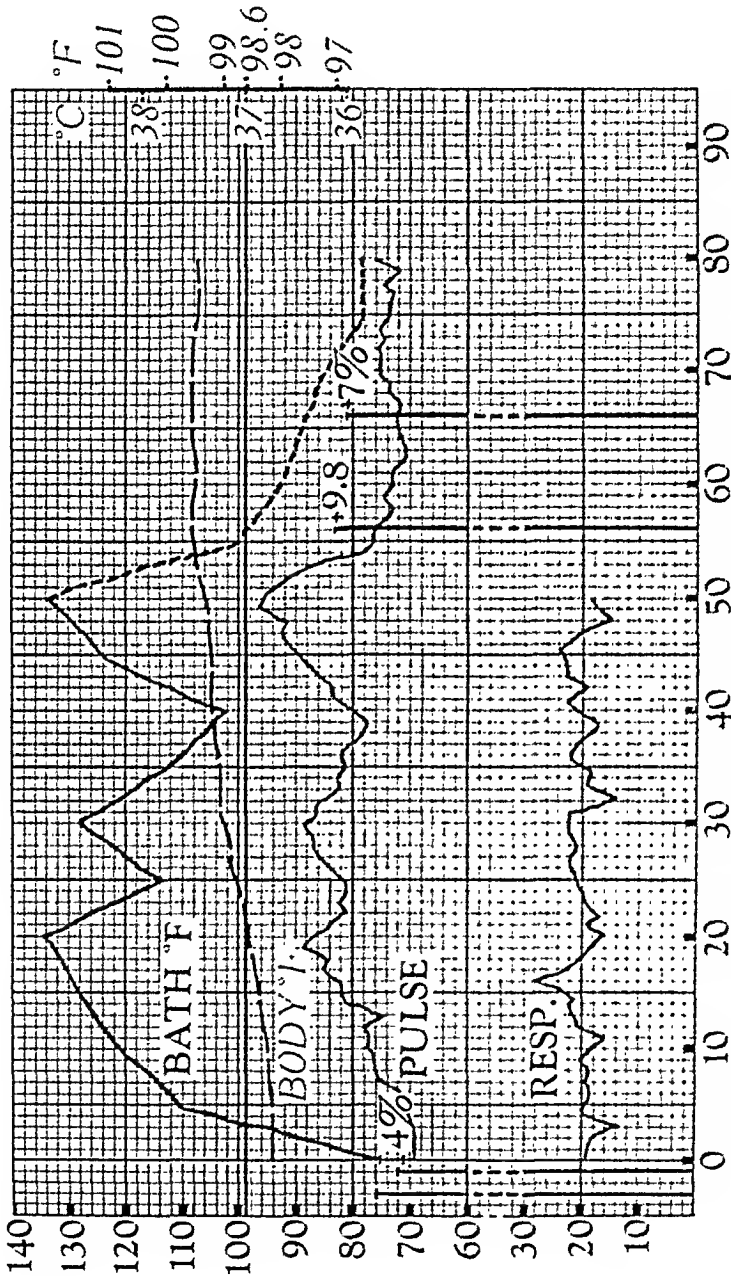


Chart 1.—Subject C. G. H., aged forty-eight years. The numbers across the bottom of the chart denote time in minutes. See legend under Chart 1 for key to the charts.

rate changes about 0.95 of a beat for each degree change in the bath (skin surface) temperature, or almost one beat for each degree.

In the following, all *decreases* in temperature were measured during ten-minute periods, while the *increases* were taken in periods varying from fifteen to forty-five minutes. This is due chiefly to the fact that these experiments were not originally designed for the specific purpose

for which we are using the results here, and the set-up was entirely dismantled before the relationships discussed here were noticed. However, the ratios, CHR/CBT, do not seem to be materially influenced by a difference in time, which, after all, might be expected, since time is not

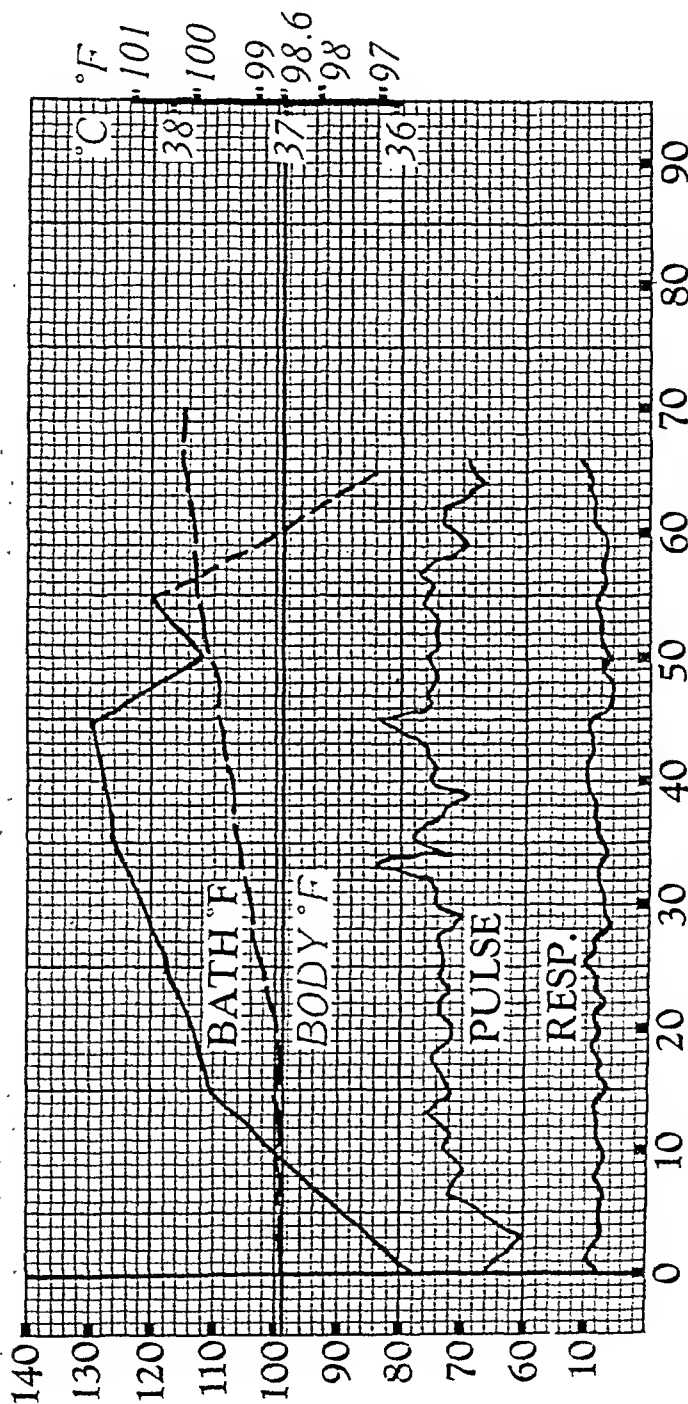


Chart 5.—Subject H. J. W., aged forty-nine years. The numbers across the bottom of the chart denote time in minutes. See legend under Chart 1 for key to the charts.

a factor in the actual calculation. The average time period for the experiments involving increases in temperature, was twenty-eight minutes.

In the tables submitted, the individuals have been grouped according to age: first, those below twenty-five years of age; second, those between twenty-five and forty years; third, those between forty and fifty-five years; and finally those above fifty-five years of age. Had we, at

the time of the experiments, become aware of the relationships indicated below, it goes without saying that more data would have been obtained from older individuals.

Any conclusion to the effect that the indicated influence of age is always present, may be questioned because of the limited number of experi-

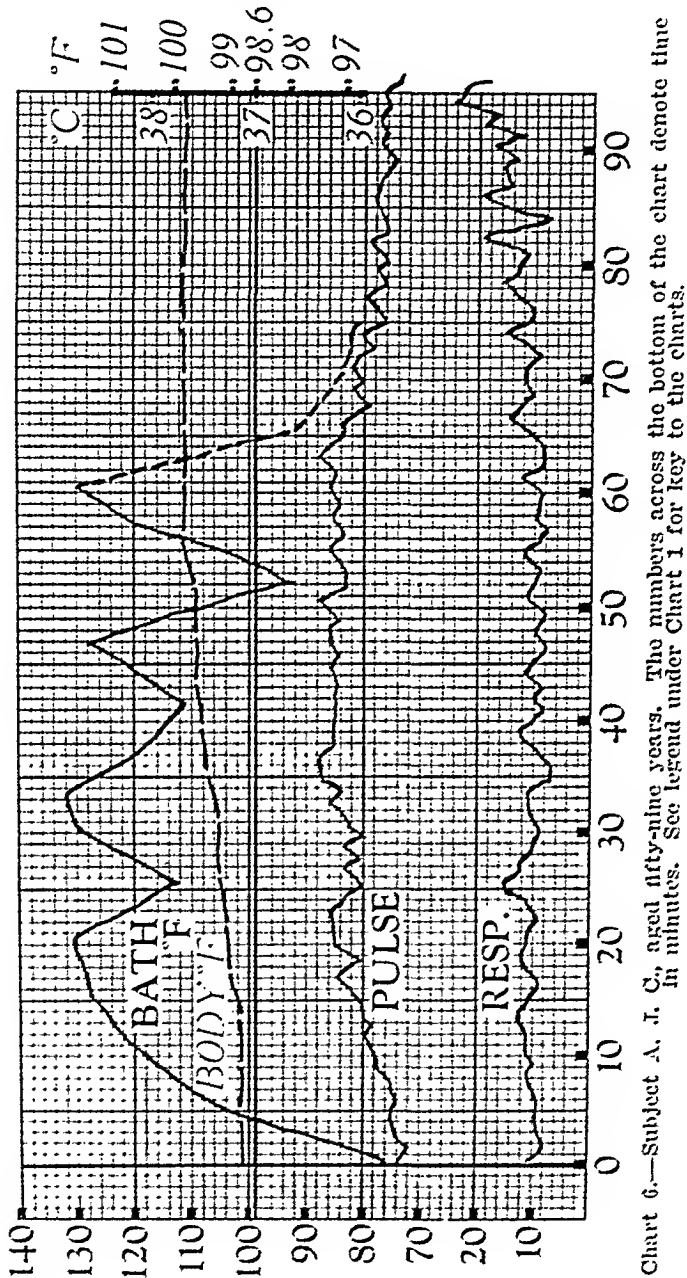


Chart 6.—Subject A. J. C., aged fifty-nine years. The numbers across the bottom of the chart denote time in minutes. See legend under Chart 1 for key to the charts.

ments conducted on older subjects, but it may also be strengthened by stating that in more than 50 experiments run upon younger subjects (athletes), none of them exhibited such a low CHR/CBT value as did the oldest subject—namely, that of 0.161. One of the lowest values obtained on a younger subject was that of 0.325, shown in the above table, on a

twenty-seven-year-old individual, and it is to a large degree upon this indirect support that we have ventured to submit our present deductions.

AGE	CHR/CBT	
20	0.945	
20	0.633	Average: 0.700
25	0.520	
27	0.325	
34	0.504	
36	0.502	Average: 0.458
39	0.502	
48	0.466	
49	0.292	Average: 0.325
59	0.161	Average: 0.161
Average: 35	0.485	

On the basis, then, of the above figures, and using the two extreme values of CHR/CBT, namely, 0.945 and 0.161, the efficiency of this skin-heart mechanism is nearly six times greater in an individual twenty years old than it is in one at the age of fifty-nine. A more correct relationship is probably to be obtained by using 0.70 to represent the value of CHR/CBT at the age of twenty, in which case it becomes 4.3 times as great as that in the fifty-nine-year-old individual.

A search of the literature has failed to reveal any information dealing with the problem of the influence of age upon the CHR/CBT ratio, although some such relationship seems to exist in the case of sinus arrhythmia,¹ a heart irregularity found more frequently in younger individuals than in older ones, and thus seems to disappear with the approach of age. In the case of the CHR/CBT relationship we are therefore forced to base our tentative deductions entirely on our own observations and upon the indirect information gathered from the literature. Upon such basis, then, it appears to us that the explanation of this marked influence of age upon the reflex efficiency, as expressed by the term CHR/CBT, may be found in some, or all of the following: (1) Greater power for compensating in the older individual; (2) A decreased efficiency, with age, of the entire reflex arc involved in the reaction; (3) A decreased sensitivity (increased threshold) in the skin temperature receptors themselves; or (4) A thickening, or drying (decreased heat conductivity) of the skin tissue surrounding the temperature receptors.

Of these four suggested explanations, the last one appears to us for the moment as the most plausible. That the threshold of the skin sensory organs increases with the thickness of the skin appears to have been long recognized. In the case of the temperature receptors, Weber³ attributes the variation in threshold to a decreased heat conductivity due to a thickening of the skin. Adrian⁴ draws a somewhat similar conclusion in regard to the sense of touch, the threshold of which depends "on the particular skin surface under the test."

Further substantiation favoring this view, is found in the anatomical condition that "There are, in man, probably no 'end organs' in the

epithelium of the skin . . .” (Waterston⁵). If the latter is correct, it seems quite self-evident that the threshold must increase with any changes in the skin structure—such as increased thickness and dryness—in fact, anything which would tend to decrease the heat conductivity of those parts of the skin which surround the temperature receptors. According to Pütter,⁶ water has a heat conductivity of 0.00135, and the dry hide of one of 0.00042; and from this he calculates the heat conductivity of the normal moist skin to be 0.00113, indicating that the heat conductivity of the skin varies directly as the moisture content. The question then arises as to whether or not such a change occurs in the human skin as the individual grows older.

Once the individual has reached maturity, the skin tends to assume a tougher and less elastic structure with increased age. There is a loss of water content which, we are told, is considered one of the chief reasons for the wrinkling of the skin. This water loss may represent but a small portion of the total skin moisture, to be sure; but if, on the other hand, it is derived chiefly from the superficial skin layer covering the temperature receptors, it may dehydrate this layer sufficiently to inhibit markedly the stimulation of the temperature receptors by external heat applications.

Such a dehydrating effect in the superficial skin layer could, in itself, be sufficient, perhaps, to explain the feebler reactions in the older individuals, but it would suffice as an explanation only in case the heat stimulus were of insufficient strength to overcome this increase in skin resistance. Should the heat stimulus be sufficiently intense to penetrate the resistance without a very great proportionate loss of strength, then one should not expect any marked difference in reaction between the moist and dehydrated skins.*

II. THE COMPARATIVE EFFECT UPON THE HEART RATE OF THE DRY AIR-RADIANT HEAT BATH AND THE WATER BATH, PER DEGREE CHANGE IN TEMPERATURE

In view of the relationship CIIR/CBT obtained in the case of the dry air-radiant heat bath, it seemed desirable to determine, if possible, the value of this relationship in the case of the water bath. For such a comparison we have tried to select the data on a basis similar to that

*As for whatever immediate value our deductions may have, we believe it will be of a clinical nature—particularly in the application of heat treatments, as well as of cold packs. Upon the basis of the data submitted, it appears that a heart rate of, say 125, may prove entirely safe in a younger individual, but quite the opposite in a man fifty or sixty years old. In other words, the truest significance of a change in heart rate, when induced by temperature changes, can be best obtained by considering such a change in rate, not only in relation to the magnitude of the temperature change but also in relation to the individual's age on a basis similar, perhaps, to that of blood pressure.

In the case of an increased heart rate from fever of infectious origin, the skin is heated from within by the circulating blood in place of from without by external media. The important factor in either case being the heating of the skin and the accompanying stimulation of the temperature (thermocouple) receptors.

upon which the data for the dry air-radiant heat bath were chosen, and from as many of the same individuals as possible. The most important omission being that the oldest subject, age fifty-nine, had not been used for the water experiments. As in the previous table, the subjects have been grouped according to age:

AGE	CHR/CBT	
19	2.4	
20	2.9	
22	3.7	
23	4.2	Average: 3.3
24	3.3	
25	3.3	
26	3.7	
27	3.8	Average: 3.6
39	3.4	
48	2.6	Average: 2.6
Average: 27	3.3	

From these results it is quite obvious that, per degree change in temperature, the water bath exerts a much greater influence upon the skin sense organs—and upon the heart rate—than does the dry air-radiant heat bath. Using the average results obtained from each medium, the relationship between their effects on the heart is found to be about seven. That is, $(\text{CHR/CBT})^w / (\text{CHR/CBT})^{\text{ha-rh}}$ equals seven. Per degree change in temperature, then, the water bath stimulates the skin sense organs as well as the heart rate, 7 times as much as does the dry hot air-radiant heat bath. In one individual, it was found to be 13 times as great. The possibilities of utilizing this marked difference in physiological effects from the two types of baths, for therapeutic as well as diagnostic purposes deserve a lengthier and more thorough consideration than can be devoted to them here.

In the case of the water bath, there appears no such distinct variation in effect, according to age, as was observed with the dry air-radiant heat bath. As previously indicated, this might be explained by assuming that the stimulation delivered by the hot water is sufficiently powerful to penetrate any increased resistance in the superficial skin layer without much loss of power. In such case, the greater resistance offered by the skin of an older individual would be insufficient to inhibit markedly the stimulation of the temperature receptors, and consequently the value of CHR/CBT would not vary with age. There appears, however, another explanation which, to us, seems equally important, especially if combined with the one already proposed. This explanation is based on the assumption that sufficient water is imbibed by the superficial skin layer to restore its heat conductivity to that of a young moist skin. This would then permit the water to deliver the heat stimulation to the skin sense organs with equal effectiveness in both young and old subjects.

Metabolic tests, when made, were taken just before and after the heat application. These tests, however, give no indication of any direct relationship between metabolism and a rise in body temperature. Indeed, in only one experiment, Chart 1, does the metabolic rate rise definitely above allowable experimental errors, and in this case the increased metabolism seems to be due more to the skin temperature than to the body temperature. One cannot fail to note the sharp contrast in the metabolic changes induced by this form of bath and those reported in our previous article⁷ on the cold douche.

SUMMARY

Under our experimental conditions, the heart rate appears to be not only affected and controlled more by the skin temperature than by the body temperature, but our results also seem to indicate that the acuity and efficiency of this control decrease with the age of the individual, depending to some degree, however, upon the heating medium used.

The efficiency factor has been derived by dividing the "change in heart rate" by the "change in bath temperature," measured in degrees Fahrenheit and is represented by CHR/CBT .

When the heating medium is a hot air-radiant heat bath, the value of CHR/CBT is about 5 times greater in a twenty-year-old individual than it is in one fifty-nine years old. The highest value obtained was from a twenty-year-old individual, namely 0.945, and the lowest value for CHR/CBT was from a fifty-nine-year-old individual, namely 0.161.

Four suggestions are submitted aiming to explain how the efficiency factor CHR/CBT may change in value with the individual's age.

In its effect on the heart rate, the hot water bath is about seven times as stimulating as is the dry air-radiant heat bath. That is, the average derived value of CHR/CBT in the dry air-radiant heat experiments was 0.475 while the average derived value from the water baths was 3.3. The effects of the water bath upon the heart rate do not seem to vary according to the individual's age, as is the case with the effects from the dry air-radiant heat bath. The reason for this appears to lie in the much greater heat stimulation delivered by the water, and to an increased heat conductivity in the superficial skin layer, in turn caused by the imbibition of water by the older dryer skins.

Upon the basis of the results obtained, it appears that the truest significance of a change in heart rate, if induced by temperature changes—water bath excepted—can be best obtained by considering such changes in relation to the individual's age, on a basis similar perhaps, to that of blood pressure.

No definite relationship was observed between the baths and the metabolic rate, and in the few cases in which an increase in metabolism was noted, such an increase seemed to be related more closely to the skin temperature than to the body temperature.

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THE CALCIFIED NODULAR DEFORMITY OF THE AORTIC VALVE*

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THIS type of cardiac disease, because of its clinical manifestations, frequency, and disputed etiology and pathogenesis, deserves more emphasis than has generally been given to it. It is frequently overlooked, and death often occurs suddenly or without marked symptoms. Many patients are never seen by a physician. Physical findings are not always constant and because of associated cardiac pain the condition is sometimes diagnosed as coronary sclerosis.

Christian¹ in speaking of this form of heart disease thought that it should be recognized clinically more frequently. He referred to it as still being considered relatively infrequently as a possibility in diagnosis. This kind of valvular disease, according to him, is characterized by the following conditions: (1) occurrence chiefly in males relatively late in life; (2) slow progress of the lesion with symptoms of cardiac decompensation appearing late, though not necessarily prolonged after they develop; (3) the presence of a thrill and harsh murmur both systolic in time, often accompanied by a diastolic murmur; (4) considerable hypertrophy of the heart; (5) often a characteristic type of pulse and normal or decreased pulse pressure; (6) the absence of anything in the latter part of the disease throwing light on the etiology; and (7) the finding at autopsy of a very heavy heart with the aortic valve greatly narrowed by thickened cusps often adherent to each other and calcified. The reports of McGinn and White,² Boas,³ and Contratto and Levine⁴ agree in general with Christian's findings.

Margolis, Ziellessen, and Barnes⁵ found that the most prominent feature in their cases with regard to symptoms was the lack of any characteristic complaints. Often symptoms referable to the cardiovascular system were absent. The findings in the patients who presented themselves with cardiac symptoms were not constant.

The frequency of this kind of heart disease and the means of diagnosing it concern the clinician chiefly. The pathologists are confronted with the task of explaining the etiology and pathogenesis of the condition. This type of valve disease, so commonly seen by the pathologist at autopsy, is obviously frequently not diagnosed clinically.

There are two beliefs concerning the etiology of the calcified nodular deformity of the aortic valve. First, there are those who are convinced

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that the lesion is degenerative or metabolic in origin. The condition is often called the atherosclerotic valve. The concept of atherosclerosis depends in general on the work of Mönckeberg⁶ who after studying aortic valves in which there was extensive calcification decided that the process bringing about the change in the cusps was the same as that found in the intima of the aorta in senile atherosclerosis. He held the opinion that the atherosclerotic process extended directly from the aorta to the valve by way of the sinus of Valsalva. His observations suggested that the change in the cusps was most pronounced at the angle where the cusps and aorta join.

Libman,⁷ Ribbert,⁸ Geerling,⁹ and Soval and Gross¹⁰ agreed with Mönckeberg in considering these deformities degenerative in origin. Soval and Gross recently, after examining hearts with this form of aortic lesion for many stigmata of rheumatic infection, failed to find the stigmata sufficiently constant to consider the change in the valves rheumatic or infectious in origin. These workers concluded that the Mönckeberg aortic lesion is purely and primarily degenerative, its occurrence and extent depending in all probability on individual predisposition to collagen involution and calcium deposition.

Representing the second belief, Clawson¹¹ from a study of 93 cases decided, from the clinical histories and gross and microscopic structure of aortic calcified valves, that the process is infectious. While atherosclerosis was not infrequently found in valves, especially the mitral, it was concluded that it is doubtful whether deformity severe enough to cause cardiac insufficiency is ever due to a purely degenerative process such as atherosclerosis.

Christian also concluded that the etiological relation of this lesion to rheumatic fever was very probable. Eleven of his 21 cases had a definite history of typical rheumatic fever from thirteen to forty-eight years before the onset of cardiac insufficiency. In two others there was an indefinite history of rheumatism. He consequently stated, "Taking all of this into consideration, a rheumatic etiology would seem highly probable from a study of these histories, a view that I have come to since my statement to the contrary in 1928 in *Orford Monograph on Diagnosis and Treatment*." McGinn and White considered it evident that aortic stenosis was doubtless often caused by infection, especially rheumatism. Boas held a similar opinion. Contratto and Levine concluded that rheumatic fever was the most frequent and most important cause of aortic stenosis.

Margolis, Ziellessen, and Barnes apparently were not convinced as to the reliability of either belief. They concluded that the etiology and pathogenesis of these valvular lesions could not be determined with certainty, but that clinical and anatomical data indicated that in some cases the lesions may have an inflammatory basis, whereas in others they may be the result of a noninflammatory degenerative process.

Since these aortic lesions have continued to be a frequent finding in autopsy material at the University of Minnesota and also at other places and because of the diversity of opinion among internists and pathologists concerning the frequency, the clinical course and findings, and the etiology and pathogenesis of these lesions, we decided to re-study our cases of nonsyphilitic aortic valve deformities, the so-called atherosclerotic valve as described by Mönekeberg. This deformity of the aortic valve was called the calcified nodular type by Clawson and Bell¹² in a former paper. This term will be used in a further description of the valve in this discussion.

The group is studied from three angles: (1) clinical characteristics; (2) frequency; and (3) etiology and pathogenesis.

CLINICAL CHARACTERISTICS

It was not possible to obtain clinical histories of all of our 200 patients. Some had died, others died suddenly without known symptoms and the amount of history obtained from some was too small for use in drawing any conclusions. The things considered in the clinical findings were age, sex, incidence of acute rheumatic fever, rate of development, sudden death, and symptoms and signs, such as dyspnea, precordial pain, thrills, and murmurs.

Age.—A clinical characteristic, commonly emphasized, is that the disease is one of old age and that most deaths occur in the older decades. The youngest in Christian's series of 21 patients was 30 years; 13 were over fifty and 7 over sixty; only 8 were under fifty. In the series of 41 reported by Margolis, Ziellensen, and Barnes only 3 were under forty years, 3 between forty and forty-nine, and 35 were fifty or more years old. Cabot's series¹³ of 27 showed 5 to be under forty years, 7 between forty and forty-nine, and 15 over fifty. It is seen in the total of these three series (89) that the majority of the patients lived to be fifty years or older. McGinn and White found their cases to be chiefly older persons. The ages in the 180 cases reported by Contratto and Levine ranged from thirteen to eighty-one years. The largest number occurred in the sixth decade.

We had 200 patients in our series. The ages are recorded in percentages in Fig. 1. One per cent of the cases was in the second decade, 6 per cent were in the third decade, 13.5 per cent in the fourth, 18.5 per cent in the fifth, 22 per cent in the sixth, 22.5 per cent in the seventh, 14 per cent in the eighth, and 2.5 per cent in the ninth. Seventy-nine per cent of the patients were fifty or more years old. The greatest number was in the seventh decade. Our findings agree with those of other observers in showing that this kind of aortic valvular lesion is found chiefly in older people.

Sex.—It has repeatedly been pointed out that the calcified deformity of the aortic valve predominates in males. Fifteen of Christian's 21 cases were found in males. In Cabot's series 25 of 28 and in that of Margolis, Ziellessen, and Barnes 34 of 42 were males. Males also predominated in the cases reported by McGinn and White and by Contratto and Levine.

We have found this greater preponderance of males to be present in our material. In 200 cases of what in our opinion would pass as the Mönckeberg aortic valve disease 165 were in males and 35 were in females. This does not give the proportion which should be expected in a cross section of the population in this locality dying with this disease, for the proportion of males to females in our autopsy material in the decades in which most of the patients died is 2 to 1. In a series of 15,937 autopsies studied by McCartney (personal communication) the number of males and females in the first three decades were practically equal. The fourth to the seventh decades, inclusive, showed the ratio of males to females to be approximately 2 to 1. Our cases of calcified aortic valve deformities should accordingly be about 165 males to 70 females, which shows the males still to be much more common in the group, a ratio of slightly over 2 to 1.

Rheumatic Fever.—In discussing the characteristics of this group, Christian gave as one point a history of rheumatism in early life. Such a history was present in 11 of his 21 cases. The rheumatic attacks occurred from thirteen to forty-eight years before the onset of cardiac insufficiency. Some had repeated attacks. A history of rheumatic fever was obtained in 23 per cent of autopsied cases and in 46 per cent of the clinical series reported by McGinn and White. Contratto and Levine found a definite history of rheumatism in 31.7 per cent of their cases. Evidences of one or more attacks of acute rheumatic fever were frequent in our series; a positive history was reported in 35 per cent. The frequency was great enough to suggest strongly a causal relationship. This is discussed more in detail under etiology.

Rate of Development.—Christian's observation that this type of aortic valve deformity develops slowly was confirmed by the clinical and pathological findings in our material. This slowness was particularly indicated by the length of time between the last attack of rheumatism and the beginning of clinical symptoms, by the large amount of calcium in the cusps and by the smooth condition of the intima of the aorta (described more fully under etiology).

Sudden Death.—The frequency of sudden death has been emphasized by Marvin and Sullivan,¹⁴ by Margolis, Ziellessen, and Barnes, and by Laplace.¹⁵ We found that sudden death occurred in 15 per cent of our 200 cases. This frequency may be unduly high, as the coroner's

antopsies were included in our material. The calcified aortic heart disease has to be considered with coronary sclerosis and syphilitic aortitis as a medicolegal cardiac case.

Symptoms and Signs.—One hundred cases with fairly good histories were selected for a study of clinical symptoms and signs.

Dyspnea was the most common symptom noted. It was present in at least 95 cases, absent in 1 and not mentioned in 4. The dyspnea was regularly of a severe degree and was frequently of long duration. Death sometimes occurred in an attack. Severe orthopnea was of common occurrence.

Laplace, Boas, and Contratto and Levine have emphasized the common occurrence of anginal attacks associated with aortic stenosis. Angina was a commonly recorded symptom in our cases. It was reported present in 42, absent in 6, and was not mentioned in 52. Coronary sclerosis was sometimes diagnosed. The theories offered to account for this cardiac pain have been interesting. Laplace, after studying the relation of blood pressure to angina, decided that a low diastolic pressure was of slight importance in the pathogenesis of angina pectoris. Boas concluded that the angina was due to the narrowing of the aortic valvular opening itself which impaired the blood supply to both coronary arteries simultaneously. Contratto and Levine thought the stenotic aortic orifice acted upon the coronary arteries in a manner similar to a common water faucet suction pump to draw blood out of the coronary arteries. A possible explanation of this pain in some cases is offered in connection with the description of the structure of the aortic cusps.

Murmurs were reported as being present in 84 of 100 cases, 30 times as both systolic and diastolic, 45 times as systolic only, and 6 times just as murmurs. In 6 cases murmurs were reported to be absent. No mention of them was made in 10.

Thrills were not so common. They were reported present in 29 and absent in 29; they were not mentioned in 42. In nearly all cases in which thrills were absent or not mentioned, findings relative to murmurs were reported.

The blood pressure readings were analyzed in 90 of our more recent cases. The following is a summary of these blood pressure readings:

<i>Height</i>	<i>Number</i>	<i>Pulse Pressure Above 65</i>
(95-150/60-90)	57	7
Above 150/60-90	10	8
Above 150/above 90	10	8
Below 150/above 90	2	0
Above 95/below 60	5	5
Below 95/70 or less	6	0
Total	90	28

Twenty of these 90 patients had a systolic pressure of over 150 and 12 had a diastolic pressure above 90. Only about 10 could be placed in the hypertensive group.

A pulse pressure of 65 or more was noted in 28 patients, usually in those with the higher readings. The pulse pressure except in a few cases was not much in excess of 65. Twelve had pulse pressures ranging from 65 to 74, eight from 75 to 84, 3 from 85 to 94, 2 from 95 to 104, one from 105 to 114, and two 155 or above.

Thirty of the 90 cases had pulse pressures which ranged from 45 to 64, about a normal reading, and 32 had pulse pressures below 45, 14 from 35 to 44, 10 from 25 to 34, 6 from 15 to 24, and 2 from 5 to 14. In general it was found that the greatest pulse pressure was in cases with less stenosis but this was not a universal finding. A high pulse pressure was not a characteristic finding in the group. Most cases had normal or low blood pressures and pulse pressures.

The clinical findings agreed in general with those reported by Margolis, Ziellessen, and Barnes, Christian, McGinn and White and Contratto and Levine except in the constancy of the presence of thrills and murmurs.

Congestive heart failure was determined by the presence of edema (indicated by anasarca, hydrothorax, or ascites) and passive congestion of the liver. Edema was noted in 75 per cent of the 200 cases and chronic passive congestion of the liver in 80 per cent.

The weight of the hearts ranged from 400 grams to 1150 grams. Most of the hearts weighed from 500 to 800 grams.

The group clearly may be considered a clinical entity. The sex and age distribution, the frequency of precordial pain and sudden death differentiate the group clinically from other forms of valve disease. Whether the group should be considered an etiological entity is discussed further under etiology.

FREQUENCY

The frequency of the calcified nodular deformity of the aortic valve concerns the clinician primarily. It has been emphasized by all the reports on this form of valve disease. The lack of a proper knowledge of the frequency of the lesion is, no doubt, the cause of some mistakes in diagnosis. The pathologist is forced to believe that adequate emphasis has not been placed upon the frequency of aortic valve lesions.

Six hundred and thirty cardiac deaths classed as rheumatic valvular disease (the calcified nodular aortic group included) were studied. These were classed as follows:

1. Acute rheumatic	78	12 per cent
2. Recurrent rheumatic	62	10 per cent
3. Healed valve deformities	490	78 per cent
a. Calcified aortic	200	41 per cent
b. Other healed valve deformities	290	59 per cent

The calcified nodular group comprized 41 per cent of all healed valve deformities or about 31.5 per cent of all rheumatic heart disease. The frequency of the calcified aortic valve deformity among the healed valve defects may be summarized as follows:

1. Total number of healed valve deformities, 490.
2. Aortic valve involved in 265, 54 per cent.
3. Number of calcified nodular aortic valve deformities, 200, which equals 75.5 per cent of all healed aortic valves.
4. Twenty-three of the remaining 65 aortic valve deformities are described as containing calcium.
5. Eighty-four per cent of all nonsyphilitic aortic valve deformities in our autopsies are described as containing calcium by gross examination.
6. The healed deformed aortic valve, a very common condition, regularly becomes calcified.
7. The calcified nodular deformity is the most common and the usual healed lesion of the aortic valve. Its importance is obvious.

ETIOLOGY

The etiology of this valve deformity was studied from two angles: (1) the infectious, and (2) the metabolic. The first is referred to as infectious or rheumatic and the latter as metabolic, degenerative, or atherosclerotic. An attempt is made to find evidence for and against each side. The etiological factors studied were age, sex, history of rheumatism, frequency of adherent pericardium, gross structure of the valves, microscopic structure of the valves and myocardium, gross appearance of the aortas, and the expectancy of healed rheumatic aortic valve deformity.

Age.—As was pointed out in studying age (Fig. 1) in its relation to the calcified aortic valve disease, it was found that the large majority of patients were old persons. Seventy-nine per cent of our cases were fifty years old or older. The largest number was in the sixth and seventh decades. Since atherosclerosis is a disease primarily of older people it becomes natural to think that the calcified aortic valves are also atherosclerotic in origin.

But, while it is true that the majority was found to die in upper age decades, it seems to us after analyzing our cases that the old age of this group has been somewhat overemphasized, especially as to etiological significance. Twenty-nine per cent of the patients were not over forty years old. Four per cent were not over twenty years old. An attempt was made in analyzing our cases to explain why people dying with this lesion are as a rule old.

In a previous study of healed valve deformities we¹² found that patients with an aortic lesion only, lived longer than those with a mitral

lesion. The ages of the 89 in the group of 200 cases of calcified nodular aortic valve deformity which had a mitral lesion also were studied and compared with the ages at which death occurred in the other cases of healed valve deformities.

Fig. 1 shows the decades in which death took place in the 89 members of the calcified aortic group with a mitral valve deformity also. It was seen that the peak of the occurrence of death dropped from the seventh decade in the total group of 200 to the fifth decade, a difference of

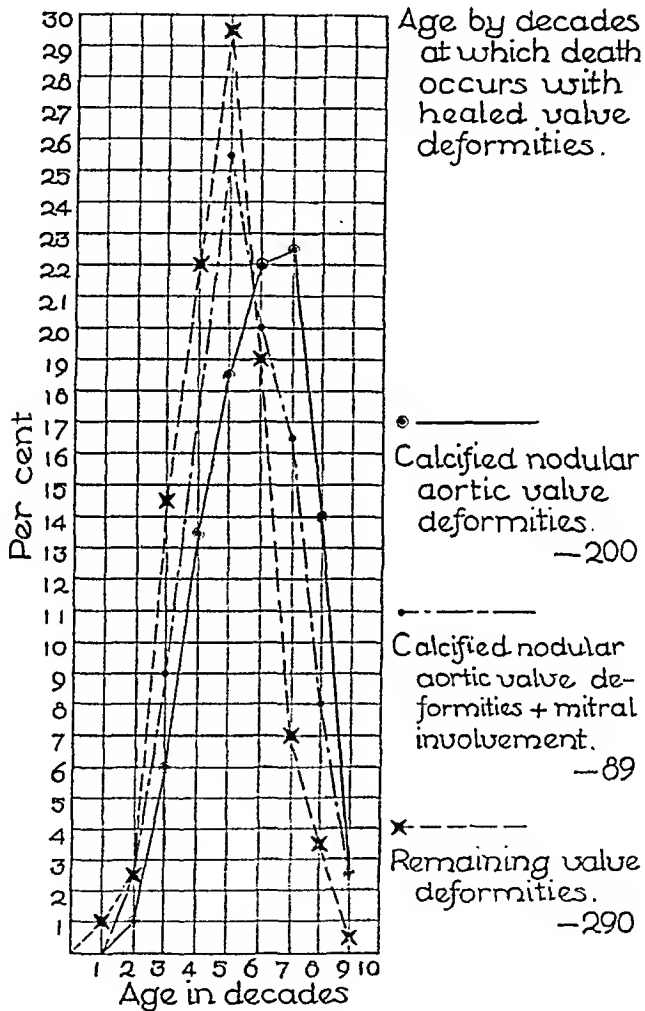


Fig. 1.

twenty years. It was also found that the greatest number of this group of 89 died in the same decade, the fifth, in which the greatest number of the remaining old valve deformity patients died. These latter are generally accepted as being of rheumatic origin. It seems reasonable to conclude that the explanation of the fact that most members of the calcified aortic group die in the older decades is that most of these people have aortic lesions alone. They live longer because they have aortic lesions rather than having aortic lesions because they are old. The fact that the members of this group are old offers no reason for believing

that the lesions in the valves in the group must be due to an etiological agent different from the agent causing the lesions in the commonly observed calcified mitral valve deformities.

Sex.—It was noted (Table I) that most people dying with a calcified aortic valve disease were males. This fact seems to have little or no significance from the etiological point of view. Atherosclerosis is of

TABLE I
SEX INCIDENCE IN RHEUMATIC HEART DISEASE, 630 PATIENTS

KIND	MALES	FEMALES	FEMALES CORRECTED
Acute rheumatic	36	42	
Recurrent rheumatic	31	31	46
Calcified nodular aortic deformity	165	35	70
Other healed valves	145	145	290
Total	377		406

about the same frequency in both sexes, though in our autopsy material death from coronary sclerosis is more common in males. The preponderance of males in this group, we think, can be explained by studying the combinations of valve involvement as related to age and sex.

The incidence of males and females in all classes of rheumatic heart disease is shown in Table I. In the acute rheumatic group (78) there were 36 males and 42 females. No correction was necessary between the sexes in this group since its occurrence was in the lower decades. Of the 62 patients dying with recurrent rheumatic endocarditis 31 were males and 31 females. This required slight correction to give a cross section of the population dying with this condition. As corrected there were 31 males and 46 females. The calcified nodular aortic group as corrected was distributed as 165 males and 70 females. The other healed valve deformities were 145 males and 290 females. The total was in the proportion of 377 males to 406 females, close to an equal distribution.

The outstanding things noted in the sex distribution in these heart diseases are: (1) males predominate in the calcified aortic group, and (2) females predominate at nearly the same ratio in cases of other healed valve deformities. These findings, we think, can be partly explained in studying the combinations of valve involvement in the rheumatic heart diseases as related to age and sex. Three combinations were studied: (1) aortic valve alone, (2) mitral valve alone, and (3) aortic and mitral valves combined.

The combinations in acute and recurrent rheumatic valvulitis are shown in Table II. The aortic valve alone occurred three times in males and not at all in the females. The mitral valve alone was present 32 times in males and 41 times in females. The aortic plus mitral combination was found 32 times in each. In this younger group it is seen

TABLE II

COMBINATIONS OF VALVE INVOLVEMENT BETWEEN THE SEXES IN ACUTE AND RECURRENT RHEUMATIC VALVULITIS, 140 PATIENTS

KIND	MALES	FEMALES
Aortic alone	3	0
Mitral alone	32	41
Aortic + mitral	32	32
Total	67	73

that there appears to be a beginning of a preponderance of aortic valve involvement alone in males and a preponderance of mitral valve involvement alone in females.

These ratios of preponderance continued to increase in the older group as shown in Table III. In this group there were 490 cases of

TABLE III

COMBINATIONS OF VALVE INVOLVEMENT BETWEEN SEXES IN ALL HEALED VALVE DEFORMITIES, 490 PATIENTS

KIND	MALES	FEMALES	FEMALES CORRECTED
Aortic alone	113	19	38 3 to 1.0
Mitral alone	91	110	220 1 to 2.5
Aortic + mitral	107	50	100
Total	311		358

healed valve deformities. Because of the decades in which death occurred the autopsy records required a correction of males to females to a ratio of 2 to 1. The combination of aortic valve involvement alone was present as 113 males to 38 females, a ratio of 3 to 1. The mitral valve alone involvement was 91 males to 220 females, a ratio of 1 to 2.5. The aortic plus mitral combination, as with acute and recurrent rheumatic valvulitis, was practically equal. The things noted were the marked preponderance of the aortic involvement in males and mitral involvement in females. The explanation of this reverse ratio is not apparent in these figures.

It was found in a previous publication that an individual with an aortic lesion would survive from fifteen to twenty years longer than one with a mitral lesion. This is probably due to the greater ability of the left ventricle to withstand strain. The fact that aortic involvement predominates in males and the mitral involvement in females and that individuals with aortic lesions live longer than those with mitral lesions offers an explanation of the preponderance of males in the calcified nodular aortic group. This explanation appears to us to be more justifiable than to assume different etiological agents in the calcified group and the group including all other healed valve deformities in the absence of a structural basis for considering them separate entities. There appears to be no basis for considering the preponderance of the male sex an etiological factor in this calcified aortic group.

Evidence of Previous Attacks of Rheumatism.—In studying the evidences of the occurrence of previous rheumatic infections in our cases five things were considered: (1) a history of rheumatism; (2) the presence of an adherent pericardium; (3) an associated mitral or other valve involvement; (4) associated gross active lesions such as acute rheumatic or bacterial vegetations on the aortic or other valves; and (5) microscopic stigmata of rheumatic inflammation in the myocardium. The findings of these five types of evidence are summarized in Table IV.

TABLE IV

EVIDENCES OF THE OCCURRENCE OF RHEUMATIC FEVER IN CASES WITH CALCIFIED NODULAR AORTIC VALVE DEFORMITY

(A) HISTORY OF RHEUMATISM AND THE PRESENCE OF PERICARDITIS				
KIND OF VALVE DEFORMITY	NUMBER	POSITIVE HISTORY	PERI-CARDITIS	ONE OR BOTH
Calcified nodular aortic	200	35 per cent	16 per cent	41 per cent
Other healed valves	160	41 per cent	18 per cent	49 per cent
(B) ASSOCIATED MITRAL OR OTHER VALVE DEFORMITY				
KIND	NUMBER	MITRAL OR OTHER VALVE DEFORMITY		
Calcified nodular aortic	200	44.5 per cent		
(C) ASSOCIATED GROSS ACTIVE LESIONS ON VALVES				
KIND	NUMBER	ACUTE RHEUMATIC	BACTERIAL	TOTAL
Calcified nodular aortic	200	8.5 per cent	4 per cent	12.5 per cent
(D) MICROSCOPIC FINDINGS IN MYOCARDIUM				
KIND	NUMBER	ASCHOFF NODULES	IRREGULAR INFLAMMATION	TOTAL
Calcified nodular aortic	54	13 per cent	24 per cent	33 per cent
Other healed valves	68	12 per cent	20 per cent	28 per cent

In 200 cases of the calcified aortic valve deformities a *history of rheumatism* was found in 35 per cent, the infection occurring as a rule many years before cardiac symptoms appeared. In 160 cases of other healed valve deformities a history of rheumatism was recorded in 41 per cent, a figure only slightly higher than that in the calcified aortic group. Several factors might account for the slightly lower incidence of a history of rheumatism in the calcified aortic group. A greater number die suddenly without any clinical history being recorded. A diagnosis of valvular disease has less commonly been made and consequently a history of rheumatism might not have been sought. Then, as pointed out by Christian, many of these people are old and do not remember having had an attack of acute rheumatic fever.

The presence of an *adherent pericardium* is significant in these cases (Table IV). Not including tuberculous pericarditis and pericardial adhesions associated with coronary thrombosis and infarction, the conspicuous cause of an adherent pericardium in autopsy material is a

previous rheumatic infection. It is seldom found without an associated valvular involvement. The frequency of an adherent pericardium was compared in this group of 200 cases of calcified aortic valve deformity and 160 other cases of healed valve deformities. Adherent pericardium was present in 16 per cent of the former and in 18 per cent of the latter. A history of rheumatism or an adherent pericardium or both was present in 41 per cent of the cases of the calcified aortic valve deformities and in 49 per cent of the other healed valve deformities. This degree of frequency of rheumatic history and adherent pericardium strongly suggested more than a coincidental relation between rheumatic infection and the calcified nodular aortic valve deformity. So high a percentage could not be found in nonrheumatic groups.

The association of a mitral or other valve deformity with the calcified aortic valve was present in 44.5 per cent of the 200 cases. There was also an association of acute rheumatic vegetations on the aortic cusps or on the cusps of other valves in 8 per cent. The bacterial type of vegetations was noted in 4 per cent. A total incidence of one or other of the active lesions was seen in 12.5 per cent (Table IV).

The myocardium was examined microscopically for rheumatic stigmata in 54 cases of the calcified nodular aortic group and in 68 cases of the other valve deformities (Table IV). Aschoff nodules were present in 13 per cent of each. Irregular inflammation was observed in 24 per cent of the former and in 20 per cent of the latter. A total evidence of inflammation was noted in 33 per cent of the calcified aortic group and in 28 per cent of the other group of healed defective valves.

The valves in the group of calcified nodular deformity were studied by gross and microscopic examination to find evidences for or against the inflammatory and degenerative origins of the changes. The following gross features were observed; (1) degree of diffuse thickening of the cusps, (2) the degree of stenosis, (3) the frequency of fusion of the cusps, and (4) the relative frequency of the calcified nodules on the aortic and ventricular surfaces of the cusps.

The degree of thickening of the cusps was expressed in grades +, ++ and +++. One plus indicated only slight thickening; three plus was an extreme grade and ++ was intermediate. One hundred and six hearts were available for this examination (Table V). No diffuse thickening

TABLE V

DEGREE OF DIFFUSE THICKENING OF AORTIC CUSPS IN CASES OF CALCIFIED NODULAR AORTIC VALVE DEFORMITY

NUMBER	DEGREE OF THICKENING	PER CENT
106	0	2
	+	15
	++	41
	+++	42
Fusion of cusps		90

was noted in 2 per cent. Grade + was present in 15 per cent, grade ++ in 41 per cent and grade +++ in 42 per cent. A severe degree of thickening of the cusps was noted in 83 per cent of the cases. The edges of the valves were fused in 90 per cent of the cases.

The amount of stenosis observed was also expressed in grades +, ++, and +++. The same 106 hearts were examined for stenosis (Table VI).

TABLE VI

DEGREE OF AORTIC STENOSIS IN CASES OF CALCIFIED AORTIC NODULAR VALVE DEFORMITY

NUMBER	DEGREE OF STENOSIS	PER CENT
106	0	8.5
	+	20.0
	++	26.5
	+++	45.0

No stenosis was present in 8.5 per cent. There was grade + in 20 per cent, grade ++ in 26.5 per cent and grade +++ in 45 per cent. Stenosis considered to be of sufficient severity to be observed clinically was present in 71.5 per cent.

The location of the calcified nodules on the valves has much significance in interpreting the pathogenesis of the calcified aortic valve. The acute verrucous vegetations regularly are found on the ventricular surface of the aortic cusps. The calcified nodules should be on the same side if the nodules are calcified vegetations. If the nodules are atherosclerotic in origin they naturally would occur on the aortic surface of the cusps. Mönckeberg believed the nodules developed in the fibrosa layer, having progressed from the aorta by way of the sinus of Valsalva. In this case the nodules being located on the aortic surfaces would suggest the atherosclerotic origin more than the inflammatory origin.

One hundred and six hearts were examined to determine the location of the nodules (Table VII). In 11 per cent the nodules were found

TABLE VII

LOCATION OF CALCIFIED NODELES ON AORTIC CUSPS

NUMBER	AORTA SURFACE ALONE	VENTRICULAR SURFACE ALONE	BOTH
106	11 per cent	1 per cent	88 per cent

on the aortic surface alone. They were on the ventricular surface alone in only one per cent of the cases. In the remaining 88 per cent calcified nodules were found on both surfaces of the cusps. These nodules are certainly not calcified vegetations. They have the gross appearance of being calcified nodular masses in the diffusely thickened valves. Their size and frequent location on the aortic surface make it possible for them

to impinge upon the orifices of the coronary arteries in some cases. It seems possible that this may in some cases be a factor in the common occurrence of angina in this group.

The microscopic findings in the cusps of these calcified aortic valves are very important in suggesting the etiology of the lesions. Two stigmata of rheumatic infection, only, were considered, exudative or proliferative inflammation and the presence of blood vessels in the cusps and rings. The cusps from 74 cases were examined microscopically (Table VIII). A definite inflammatory reaction was noted in 69 per

TABLE VIII

MICROSCOPIC FINDINGS IN THE AORTIC VALVE IN CASES OF CALCIFIED NODULAR AORTIC VALVE DEFORMITY

NUMBER	INFLAMMATION, PROLIFERATIVE OR EX- UDATIVE	BLOOD VESSELS, VALVE- RING OR BOTH	TOTAL
74	69 per cent	95 per cent	97 per cent

cent. The type of reaction was mostly proliferative. It may be believed, of course, that this inflammation is a foreign body reaction to the calcium. Against this is the fact that calcium was present in all cases but evidence of an active inflammatory reaction was found in only 69 per cent of the cases. It was also noted that the position of the inflammatory reaction bore no immediate relation to the position of the calcium. Often the most pronounced inflammation was seen in parts of the scar where there was no calcium. The calcium was imbedded in a scar much of which was old and healed. The amount of active inflammation was practically the same as that seen in healed thickened mitral valves.

Whether blood vessels are present in normal valves has been a point of disagreement among workers for several years. Gross,¹⁶ who has studied this subject extensively, has decided that blood vessels are not present in normal valves. All observers agree that vessels are not found by microscopic examination in the normal valves. There is not a general agreement on whether vessels may be demonstrated by injecting the valves. Seventy-four of these thickened aortic valves were examined and definite blood vessels were observed in the cusp or ring or both in 95 per cent of the cases (Table VIII).

In the 74 hearts 97 per cent showed evidence of inflammation by the presence of an inflammatory reaction or blood vessels in the valves or valve rings or by both.

Cholesterol crystals so commonly seen in atherosclerosis were not seen in any of the valves. Lipoid material in small amount was sometimes seen.

Another gross observation made referable to etiology, was the smooth condition in the intima of the arch of the aorta in these cases. If the

lesions in the valves are atherosclerotic in nature and are extensions from the intimal change in atherosclerotic aortas, one should find considerable intimal change in the aortas of this group. The arches of the aortas were examined in 106 hearts (Table IX). In 86 per cent there was no sclerosis

TABLE IX

DEGREE OF ATHEROSCLEROSIS IN AORTA IN CASES OF CALCIFIED NODULAR AORTIC VALVE DEFORMITY

NUMBER	NONE TO A TRACE	MODERATE	EXTREME
106	86 per cent	14 per cent	0

or only a trace. Fourteen per cent showed a moderate amount of intimal atherosclerosis. Extensive atherosclerosis was not seen in any. The smoothness of the arches of the aortas in these cases was a conspicuous finding. No other group of individuals in the same decades of age could be found with so little atherosclerosis. In fact, it seems evident that these aortas have been protected by the stenosis of the aortic orifice and since the smoothness corresponds to that in young people, it is strongly suggested that the deformities in the cusps in most cases began early in life and have been present a long time. This pathological inference is in harmony with the clinical observations noted by many. This anatomical observation not only indicates an early occurrence of the change in the valve but it fails to support the idea that the valvular lesion is atherosclerotic in origin.

Another approach to the study of the etiology of these calcified aortic cusps is to study the expectancy of healed valve deformities from the incidence of acute and recurrent valvulitis both of which, of course, are obviously of rheumatic origin. An illustration of this study is seen in Fig. 2.

Exclusive of syphilitic and bacterial valvulitis there were 630 cases of valvular disease (acute rheumatic valvulitis, recurrent rheumatic valvulitis and healed valvular deformities). The acute and recurrent rheumatic cases (140 in number) were placed in one group since there can be no doubt about the rheumatic etiology. The total healed valve deformities (490 in number) were placed in a second group. The frequency of aortic involvement was studied and compared in the two groups.

In the acute and recurrent rheumatic group the aortic valve alone was involved in 2.1 per cent of the cases. The total aortic involvement in this group was 49.2 per cent. In the group of healed valves the aortic valve alone was involved in 26.3 per cent and the total aortic involvement was 59.1 per cent of the 490 cases.

The healed valve group had a 10 per cent greater incidence of aortic involvement than the acute and recurrent rheumatic group. This dif-

ference can probably be accounted for by the increase with age in the involvement of the aortic valve alone. The chance of aortic involvement alone increases with age as shown in Fig. 2. In this chart it is seen that the individuals in the healed valve group had an average age of about thirty years older than those in the acute and recurrent rheumatic group. It appears evident that the incidence of the total healed aortic valve deformities is practically what should be expected from the incidence of aortic involvement in known cases of rheumatic infection. If the calcified aortic group (200) were taken out of the total healed valve group (490) it would leave a relatively small number (87) having an

Aortic involvement at death.

Kind	Number	Aortic alone	Total aortic
Acute and recurrent rheumatic	140	2.1 %	49.3 %
Total healed valve deformities	490	26.3 %	59.1 %

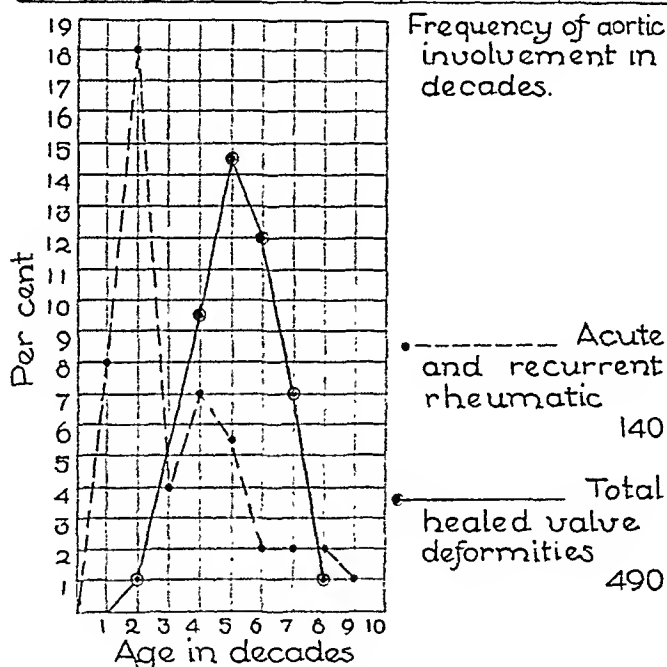


Fig. 2.

aortic lesion. The number with aortic involvement would be much below what should be expected. There seems to be no reasonable necessity to look for a nonrheumatic cause of the calcified aortic valve deformities.

COMMENT

The calcified aortic valve deformity is a condition which is being recognized and emphasized more by both internists and pathologists. The condition has come to be looked upon as a clinical entity. This is primarily because of certain common clinical manifestations, such as being more common in males and in the older groups. It is also characterized by the clinical symptoms often appearing many years after the probable

beginning of the disease. The pulse pressure commonly is not high. It carries with it a better prognosis than a mitral disease, since the right ventricle is not handicapped so easily. It has to be differentiated from coronary sclerosis on account of the common occurrence of angina and sudden death.

Physical findings when present are fairly characteristic but are not always constant.

The fact that this type of aortic valve disease is a clinical entity does not necessarily indicate that it is an etiological entity.

Aortic valve disease, especially calcified aortic stenosis, is a much more common condition than has been generally believed. The condition is being diagnosed clinically much more frequently than was done ten to fifteen years ago. It is much more common than a nonsyphilitic aortic valve deformity without calcium. In fact, calcification is the usual finding in a healed scarred aortic valve.

The exact etiology and pathogenesis of this type of lesion cannot be proved conclusively any more than the etiology and pathogenesis of the sclerotic and calcified mitral valve in which calcification is practically as common. The origin of the mitral deformity is generally accepted by most students of the subject to be due to previous and probably repeated rheumatic infections which cause a proliferative inflammation which terminates in a scar. It is not unreasonable to accept the same explanation for the etiology and pathogenesis of the calcified aortic lesions.

Two theories are advanced to explain the origin of these calcified aortic valve lesions; (1) the metabolic, degenerative or atherosclerotic, and (2) the infectious or what is generally called rheumatic.

The age of most of the individuals in the group, sixth and seventh decades, has supported the atherosclerotic theory in the opinion of many. On the other hand it has to be remembered that this is an aortic lesion and people with aortic lesions live longer than those with mitral lesions. It was found that those in the calcified aortic group who had mitral lesions also died, as a rule, in the same decades as other cases of healed valvular deformities which are commonly recognized as being due to rheumatic infection.

The greater number of people having this calcified aortic valve deformity are males, a fact also sometimes considered to be in favor of the atherosclerotic theory of etiology. This also fails to have much weight when it is remembered that females have atherosclerosis about as commonly as males and also that the aortic valve involvement is more common in males than in females and the mitral valve involvement is more common in females than in males. The males having the preponderance of aortic valve involvement live longer, and the females with the pre-

ponderance of mitral involvement die earlier and thus the calcified aortic valve deformity becomes a disease of males primarily in the older groups.

The rheumatic origin of this calcified aortic lesion is strongly supported by the various evidences of one or more attacks of acute rheumatic fever in the members of the group. A positive history of rheumatic fever was practically as common in this group as in other cases of healed valve deformity. The presence of an adherent pericardium was essentially the same as in cases with other healed valve defects generally recognized as being rheumatic. Aschoff nodules and other microscopic stigmata of rheumatic inflammation were found with equal frequency in the group with the calcified aortic cusps and in the group with healed valve deformities not so classified.

The gross structure of the aortic valves was not characteristic of an atherosclerotic process but was in all respects similar to the structure of the calcified mitral valves. The calcified nodules appeared to develop in the scar and project outward usually on both surfaces of the valve. The nodules were large enough apparently to impinge in some cases upon the coronary orifices. This may explain the frequent cardiac pain in some of these cases. The cusps were diffusely thickened and their edges were fused. Stenosis to a marked degree was common. The entire process appears to be the end-result of inflammation, probably rheumatic.

Microscopically, the valves showed the presence of an inflammatory reaction or blood vessels or both in nearly all cases. The inflammatory reaction bore no immediate relation to the calcium. The fact that calcium without any proliferative or exudative inflammatory reaction was present in 31 per cent of the cases suggested that the inflammation was not a foreign body reaction to the calcium.

The degree of smoothness in the aorta gave no support to the theory that the thickening of the cusps is due to atherosclerosis. These aortas rather appeared to have been protected by the aortic stenosis and suggested that the valvular disease began early in life.

When the incidence of aortic valvular involvement in cases of acute and recurrent rheumatic endocarditis was compared with the incidence in the group of all old healed valve deformities it was seen that the aortic involvement in the latter was about what should be expected. If the calcified group were not included among the rheumatic healed valve defects there would not be a sufficient number of aortic valve deformities to meet the expectancy. A cause other than rheumatic infection is not necessary to explain the frequency of healed calcified aortic valve disease.

It seems reasonable to conclude that the calcified nodular aortic valve deformity is of common occurrence, that it is the most common healed aortic lesion and that the change in the valves is due to repeated attacks of rheumatic proliferative inflammation with calcification similar to that so commonly seen in the mitral cusps.

SUMMARY

1. The calcified nodular deformity of the aortic valve with stenosis is a clinical type frequently not diagnosed because of the common occurrence of sudden death and the lack of constancy of clinical symptoms and signs and because the clinical symptoms are often similar to other types of heart disease such as coronary sclerosis.

2. This lesion is a common one. It is the usual kind found in healed aortic valve deformities. The healed thickened aortic valves as well as the mitral valves commonly undergo calcification.

3. The available evidences in our material relative to etiology support the rheumatic origin of the lesion rather than the degenerative or atherosclerotic origin.

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THE INFLUENCE OF THE SIZE OF CARDIAC INFARCTS UPON THE ELECTROCARDIOGRAM*

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A VOLUMINOUS literature now exists on the use of the electrocardiogram to determine the location of a clinical cardiac infarct. The types of electrocardiograms produced by the occlusion of the right coronary artery or the left; of infarction located in the right or left ventricle, on the anterior or posterior surface of the heart, or involving one or another of the cardiac muscles, have been explored extensively in experimental and clinical investigations.

The size of the infarction in any location is undoubtedly a matter of considerable prognostic importance. At the present time, the size is inferred chiefly from the severity of the clinical symptoms, it being assumed that severe symptoms of collapse, high fever, cardiac failure, indicate a large infarction, and mild symptoms a small one. Satisfactory information as to the accuracy of this inference does not exist, although it is probably correct in the majority of cases. However, there are several factors which may disturb a parallelism between the severity of symptoms and size of infarction, such as the number of previous occlusions, reflex vasomotor changes, the state of the remainder of the cardiac circulation at the time of an infarction. The extent to which the electrocardiogram can be put to use in judging whether an infarct is large or small has received relatively little attention.

In the hope of throwing some light on this question, we have analyzed the electrocardiographic data from a study in which a large coronary vessel was ligated and the size of the resulting infarct was measured.

METHOD

The circumflex branch, without the vein, was ligated at its origin from the left coronary artery, in 42 cats. These animals were employed in another study of the effect of aminophylline on the size of a cardiac infarct. Of the entire group, 11 died in from four to seventeen days, and 31 survived longer and were killed three weeks after the ligation. The size of the resulting infarct was measured with a planimeter at the autopsy. For the details of the operative technique, the original

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paper may be consulted.¹ Electrocardiograms (3 standard leads) were taken just before the operation, within about ten to thirty minutes after the ligation, the following day, and every third day thereafter.

RESULTS

The resulting infarction was located on the posterior surface of the heart, involving chiefly the left ventricle. Its circumference was fairly sharply demarcated; its form was irregularly triangular, with its base along the auriculoventricular groove, and its apex extending downward toward the apex of the heart. It showed wide variations in size, from 2.26 to 12.84 sq. cm.

The only electrocardiographic changes that could be correlated with the size of the infarct were the displacement of the R-T or S-T seg-

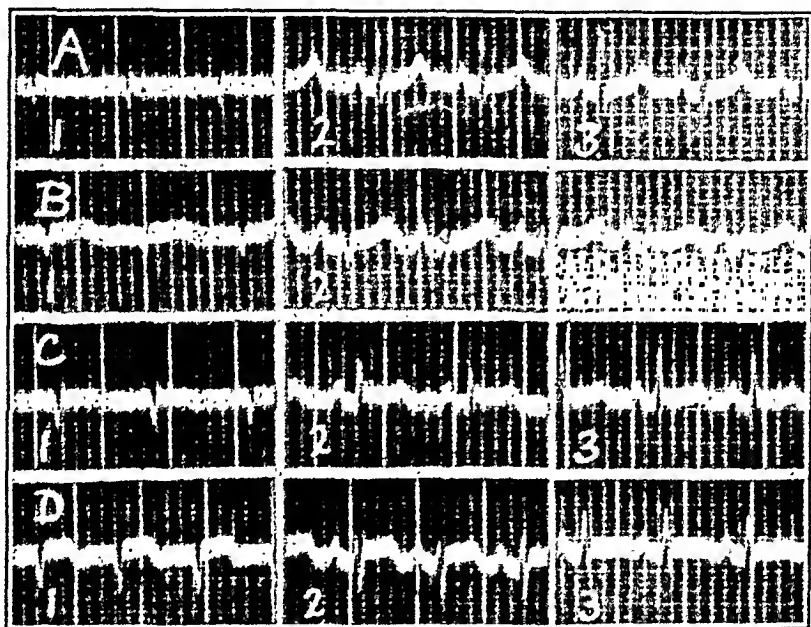


Fig. 1.—Displacement of R-T or S-T segments due to purulent pericarditis in cat with control operation in which the coronary artery was not ligated. (A) Before operation; (B) 18 minutes after operation; (C) second day; (D) seventh day.

ments, and ventricular tachycardia. Slight displacement of the segments (about 0.5 mm. or less) was sometimes present in the control tracing, and this was taken into account in judging the effects of infarction. Changes in the T-waves were not reliable, as shown by a control series of 13 animals in which the operation was carried through in all its details, except for the ligation of the artery. Electrocardiograms taken immediately after the operation and again at the usual intervals throughout the twenty-one days of study, when compared with the preoperative tracing, showed marked changes in the T-waves and the forms of the QRS groups; a negative T-wave in Leads I or II or both, became isoelectric or positive, and vice versa. The change appeared immediately after the operation, or at some time during the

next thirteen days. In one animal a coupled rhythm, due to premature ventricular contractions, appeared on the twenty-first day. Whether these changes are due to the displacement of the heart as a result of the thoracic operation cannot be stated. It is known that T-wave changes and premature ventricular contractions occur spontaneously in cats.² In only two animals did the control operation result in the displacement of the R-T or S-T segment; in one of these on the seventh day, without any apparent explanation at autopsy, in the other apparently on the basis of a purulent pericarditis (Fig. 1).

The results are presented in Table I. Among the 42 animals with a posterior infarct as the result of the ligation of the entire circumflex branch of the left coronary artery 11, or 26.6 per cent, failed to show any displacement of the R-T or S-T segments in the standard three leads of the electrocardiogram. The infarct in the 11 without this change was about one-half to two-thirds as large as in the 31 in which the change was present. In general, also, the more pronounced

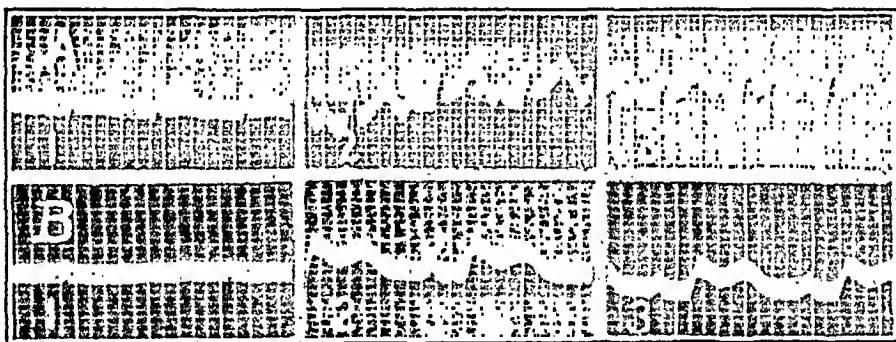


Fig. 2.—Type of R-T change with infarct of average size and with very large infarct. (A) Cat 27T. Infarct of average size, 6.97 sq. cm. (B) Cat 24T. Very large infarct, 12.84 sq. cm.

changes in the R-T or S-T segment were produced by the larger infarcts. The types of changes produced by the infarcts of average size and by the larger ones are shown in Fig. 2. Individual differences were considerable, however, and, as illustrated in Fig. 3, of two animals having an infarct of the same size, one showed almost no change in the R-T or S-T segment, while in the other, the change was quite marked.

In all animals in which displacement of the segments occurred after the ligation (31, or 73.4 per cent, of the 42 animals), a considerable degree of restitution took place within twenty-four hours, although some displacement was still present at the end of the three-week period in 22 or 71 per cent of the 31 animals in which displacement had occurred. In nine animals in which the R-T segment was restored to normal earlier, the sizes of the infarcts were similar to those in which the change persisted beyond the three-week period, the largest as well as the smallest infarct being represented in this group. The size of

TABLE I

THE RELATION OF THE SIZE OF THE INFARCT TO THE ELECTROCARDIOGRAPHIC CHANGES

CAT NO.	DISPLACED R-T OR S-T		1+ CHANGE	2+ TO 5+	VENTRICULAR TACHY- CARDIA	RESTITUTION OF DIS- PLACED R-T OR S-T SEG- MENT BEFORE 3 WEEKS
	NO	YES	(0.5 TO 1 MM.)	CHANGE (MORE THAN 1 MM.)		
	(SQ. CM.)	(SQ. CM.)	(SQ. CM.)	(SQ. CM.)	(SQ. CM.)	(SQ. CM.)
1		9.48		9.48		
2		7.74		7.74		
3		7.36		7.36		
4		7.29		7.29	7.29 (post-operative)	7.36 (19)†
5		6.97		6.97		
6		6.32	6.32			6.97 (19)
7	6.07					
8		5.94		5.94		
9	5.61					
10	4.45					
11		4.19	4.19			4.19 (17)
12		3.94		3.94		
13		3.74	3.74			3.74 (8)
14	3.36				3.36 (2)†	
15	2.65					
16	2.58					
17		2.26	2.26		2.26 (8)	2.26 (19)
18 (5)*		7.36		7.36		
19 (9)		5.94		5.94		
20 (4)		5.87	5.87			
21 (17)		5.48		5.48		
22 (11)		4.32	4.32			
23 (14)		2.65	2.65			
24T		12.84		12.84	12.84 (8)	12.84 (17)
25T		9.81		9.81		
26T		9.10	9.10		9.10 (21)	
27T		6.97		6.97	6.97 (2)	6.97 (13)
28T		6.97		6.97		
29T		6.90		6.90		
30T		5.94		5.94	5.94 (post-operative)	5.94 (15)
31T	5.74					
32T	5.29				5.29 (10)	
33T	3.68					
34T	3.55				3.55 (2)	
35T		3.23	3.23			3.23 (17)
36T	3.23				3.23 (2)	
37T		2.90		2.90		
38T (6)		9.68		9.68		
39T (8)		8.39		8.39	8.39 (5)	
40T (13)		8.00		8.00	8.00 (2)	
41T (8)		6.45		6.45		
42T (8)		5.61		5.61	5.61 (2)	
Total No.	11	31	9	22	13	9
Range	2.58 to 6.07	2.26 to 12.84	2.26 to 9.10	2.90 to 12.84	2.26 to 12.84	2.26 to 12.84
Average	4.20	6.44	4.63	7.18	6.30	5.94
Median	3.68	6.45	4.19	6.97	5.94	5.94
Mode	3.23 to 3.68	5.87 to 6.97	--	5.94 to 6.97	3.23 to 3.55	--

*Figures in parentheses in this column indicate number of days animal survived the operation.

†Figures in parentheses in this column indicate day after operation when ventricular tachycardia was first seen.

‡Figures in parentheses in this column indicate approximate duration, in days, of displacement of R-T or S-T segment.

(T) Treated with aminophylline 25 mg. per kg., daily, intramuscularly. The treatment was without influence on the size of the infarct, and the two groups were treated as one (1).

the infarct, if it exerts any influence at all, therefore, does not appear to be the sole factor determining the speed of restitution of the displaced R-T segment.

Ventricular tachycardia occurred in 13 animals (31 per cent of the cases), appearing at various times from immediately after the ligation to twenty-one days later. As pointed out in the previous study,¹ the use of aminophylline in many of these might have contributed to the high incidence of ventricular tachycardia. The most frequent size, as well as the average size, of the infarct in those which showed a ventricular tachycardia was essentially the same as in those without it, and the range of infarct sizes in this group covered almost the whole range of infarct sizes in the group without the abnormal rhythm.

In those that were unable to survive the effects of the ligation for as long as three weeks (indicated by the length of survival in the table), the infarct was no larger than in the group that survived longer periods (range of sizes 2.65 to 9.68 sq. cm.; average 6.34; median

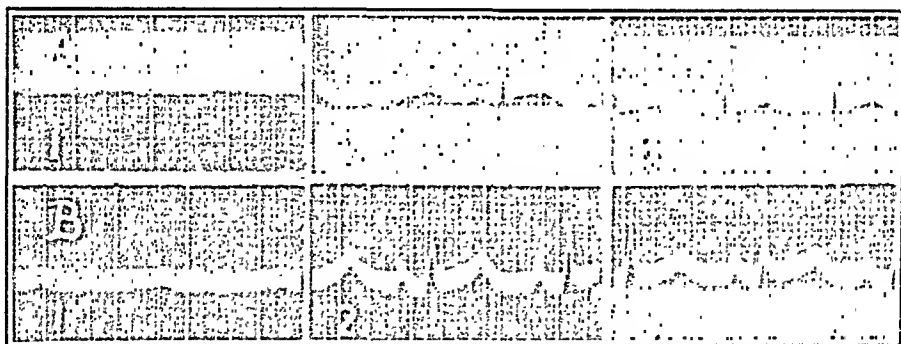


Fig. 3.—Individual differences in R-T changes in case of infarcts of similar size. (A) Cat 20; almost negligible displacement; infarct 5.87 sq. cm. (B) Cat 8; fairly marked displacement; infarct 5.94 sq. cm.

5.94; mode 5.48 to 5.94). Factors other than the size of the infarct, therefore, play an important rôle in the duration of survival of an even apparently normal animal, after a coronary occlusion. All the 11 animals which failed to survive three weeks developed R-T or S-T displacements, and in 8 of these, the changes were very marked.

SUMMARY AND CONCLUSIONS

The occlusion of the entire circumflex branch of the left coronary artery (without the vein) in cats caused an infarct of fairly uniform location but of varying size. The electrocardiographic changes were correlated with the different sizes of the infarcts. The results show that: (1) A fairly large proportion (about 25 per cent) may show no R-T or S-T segment displacement. (2) Those which fail, under these circumstances, to develop displacement of the R-T or S-T segments are likely to have the smaller infarcts, and those showing the greatest degree of displacement are likely to have the largest infarcts. (3) Differences in the speed of restitution of the displacement of the R-T or

S-T segment do not indicate differences in the size of the infarcts. (4) The occurrence of ventricular tachycardia throws no light on the size of the infarct, it being present after small as well as after large ones. The ventricular tachycardia therefore appears to depend chiefly upon a focus of irritation rather than upon its size. (5) Individual variations are very marked, and infarcts of the same size may be found in all the groups, among those showing no displacement of the R-T or S-T segments, among those showing slight or marked displacement, among those with, and those without ventricular tachycardia.

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RESPIRATORY CHANGES PRODUCED IN THE CARDIAC
PATIENT BY REBREATHING EXPERIMENTS AS
COMPARED WITH THOSE OF THE
NORMAL INDIVIDUAL*†

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FOR many years workers in the field of experimental medicine have been concerned with devising a method that would quantitatively differentiate, in degree of severity, the cardiac patient from the normal individual. All the muscle exercise tests that have been used suffer from the fact that the individual musculature is a variable which defies quantitation. Furthermore, estimations of change in blood pressure, respiratory rate, and pulse rate are in themselves very gross methods of differentiation. The respiratory rate is not an index of the amount of air handled by the patient.

The fact that the cardiorespiratory system must be considered as a unit is a concept long recognized by the physician. It was the realization of this unity and the belief that the substitution of a progressive anoxemia for muscular exercise would give us a method by which a direct quantitative burden could be placed on the cardiorespiratory system, that led us to investigate the effects of this procedure on the normal and on the cardiac patient.

Our method of investigation was definitely influenced by previous work, the review of which will explain our subsequent approach to the subject. Without delving into the enormous amount of literature dealing with the regulation of the respiratory system, we believe that it can be definitely stated that progressive anoxemia brings into play several compensating mechanisms in the cardiorespiratory function of the body. These compensatory mechanisms are as follows:¹

A. Progressive anoxemia per se causes increased ventilation of the lungs. More than a decade ago the British Hemoglobin Committee of the Medical Research Conference² reported that "the want of oxygen must be regarded as having a direct effect on the respiratory center, and it does not matter whether we regard that effect as due to an actual

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stimulating property of oxygen deficiency or to an increase in the sensitivity of the respiratory center to the hydrogen ion." The modern concept of this phenomenon is summarized by Y. Henderson, and Radloff.³ It is as follows: "Oxygen deficiency through some nonacidotic process increases the sensitivity of the respiratory center to its specific stimulus; the hydrogen ion concentration of the blood plasma." Schneider⁴ has also shown that in rebreathing experiments, when the oxygen is depleted and the carbon dioxide is filtered out, the depth of

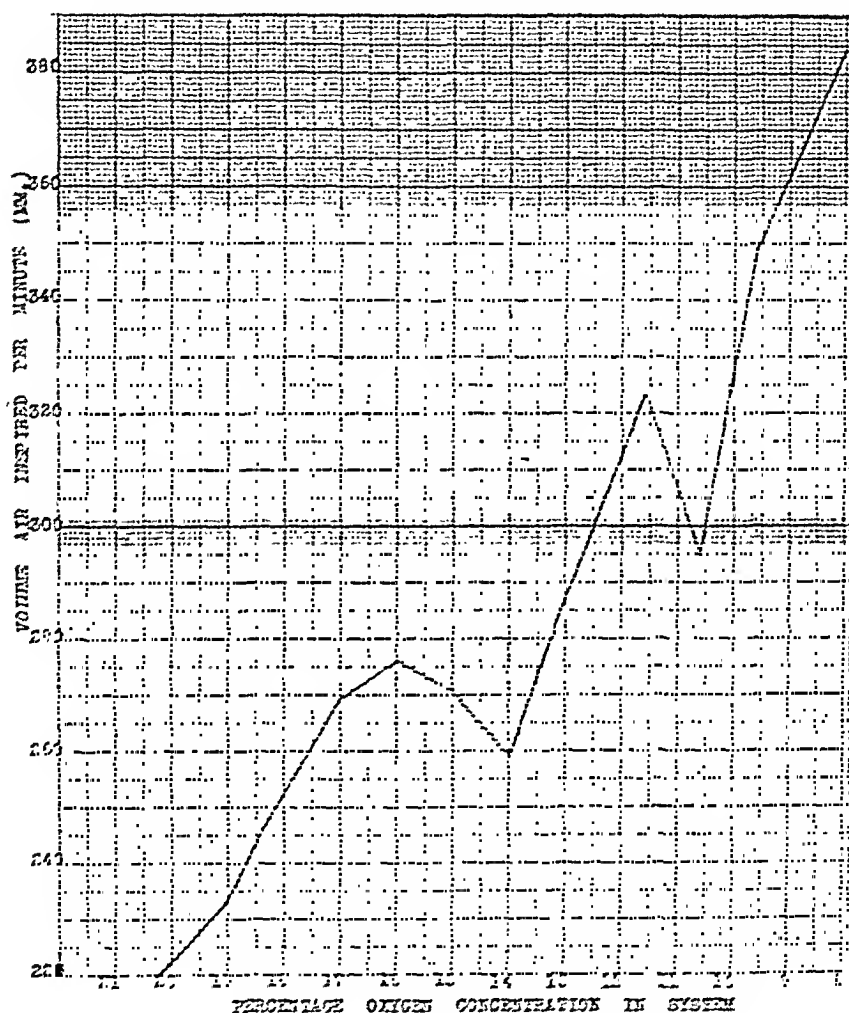


Fig. 1.—M. R., aged twenty-four years (normal).

the respirations tends to increase rather than the rate. Thus we see the effect of anoxemia on the respiratory system per se.

B. The second compensatory mechanism, according to Wiggers,⁵ is brought about by the resultant hyperpnea which has the value of elevating the blood oxygen tension. This is accomplished by a greater admixture of the air in the spirometer with the alveolar air. In addition to this there is evidence which points to the opening of previously unused or partially-used alveolar spaces, thus allowing for a better

equilibrium between the alveolar and the blood gases. However, because of the decreased dissociation of oxyhemoglobin in the associated hypocapnic state the benefit of the hyperpnea is considerably less than may be inferred.

C. The third compensatory mechanism,¹ namely the increase in the number of circulating red cells which occurs as the result of anoxemia, cannot be of as great importance as one might infer. True, more oxygen

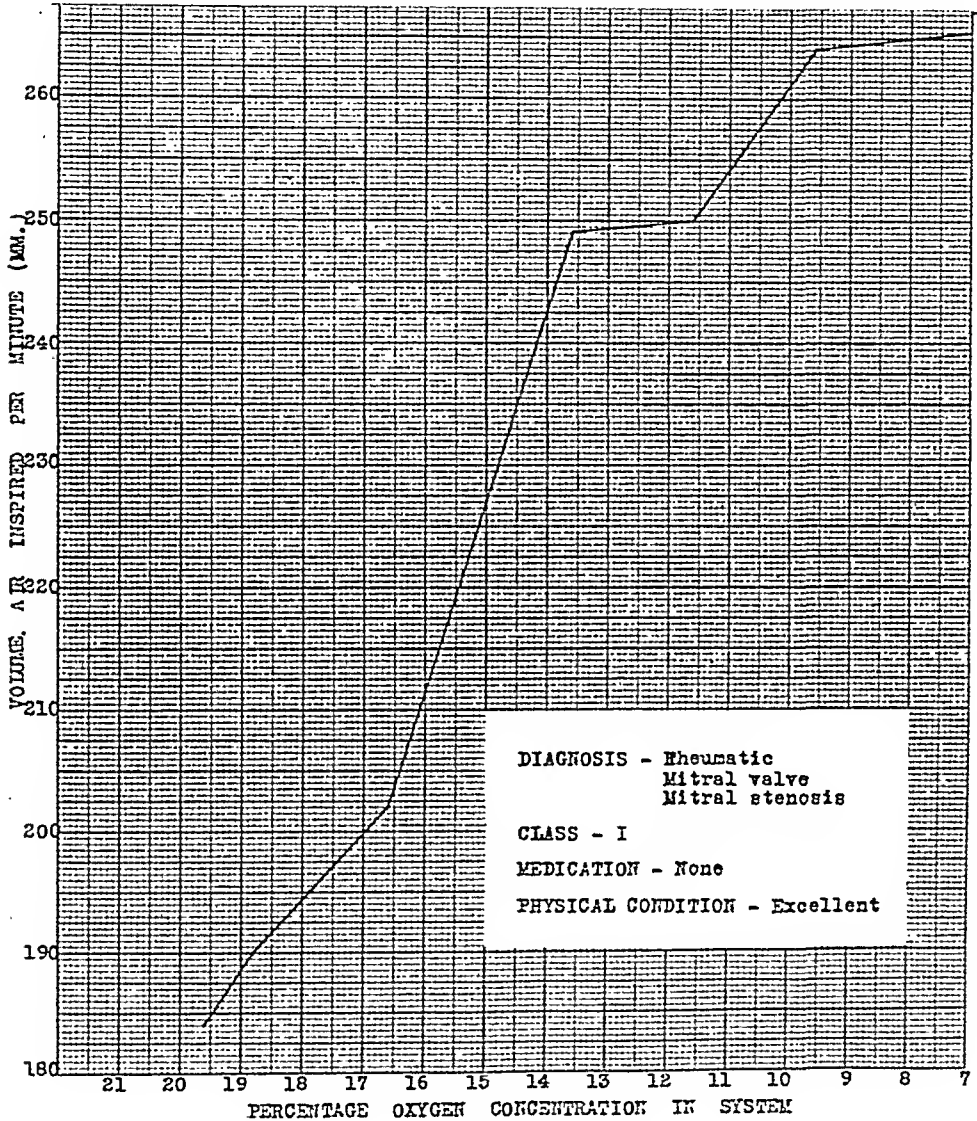


Fig. 2.—V. A., aged eighteen years (cardiac).

is carried to the capillaries as a result of this mechanism, but we must bear in mind that it is the partial pressure of this gas that is of the greatest importance. Haldane and Barcroft⁵ state that the increased volume of the transported oxygen may keep the partial pressure of the gas from falling as rapidly as it might otherwise do.

D. The fourth compensatory mechanism⁶ is that of increased cardiac output. Recent studies have shown that the cardiac rate is accelerated and the heart forces are increased when the oxygen reaches about 14 per

cent. These reactions are greatly increased when the oxygen reaches 12 per cent or 11.5 per cent. Furthermore, the diastolic size of the heart increases and the muscle output is augmented.⁷ In addition to this the arterial pressures rise and the pulse pressure tends to become greater.⁷ Wiggers suggests that this mechanism accomplishes what the three other mechanisms accomplish imperfectly.

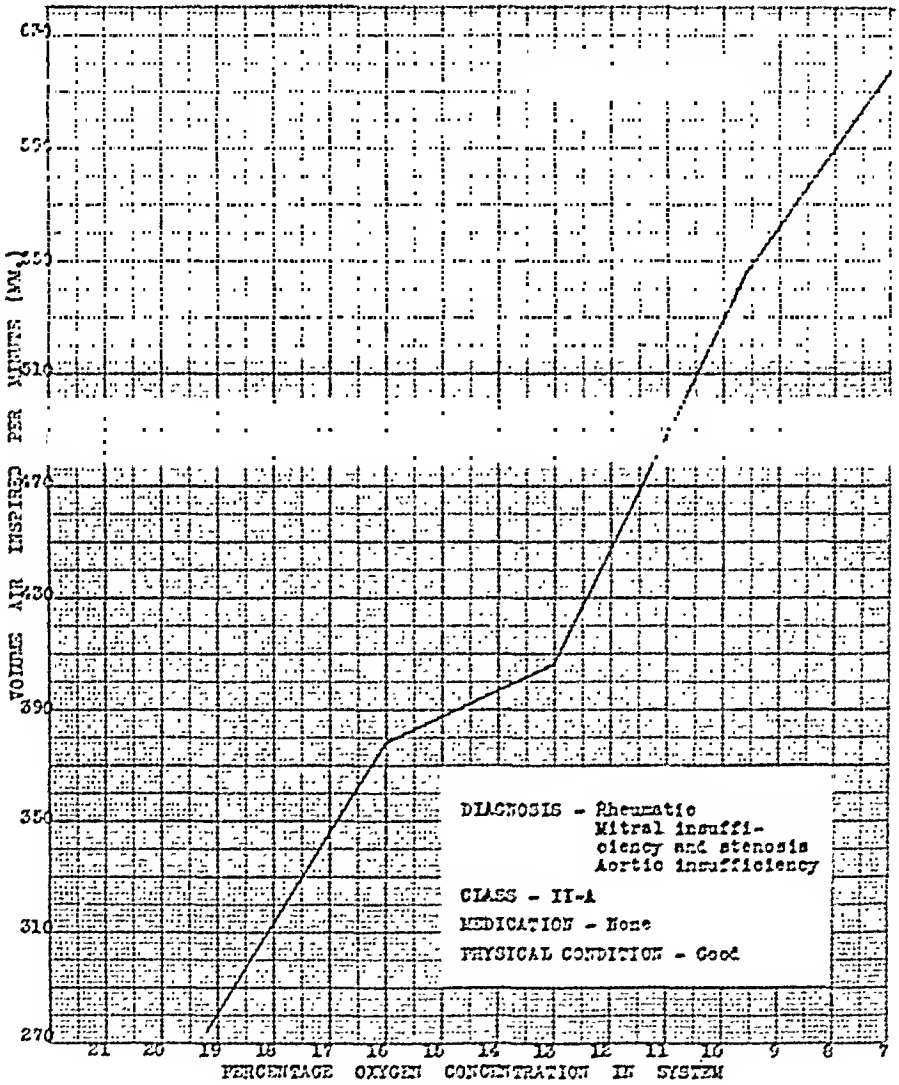


Fig. 3.—W. F., aged twenty-two years (cardiac).

As a result of the observations just quoted it was our premise that the cardiorespiratory system of the cardiac patient could not respond with the facility of that of the normal individual when subjected to decrease in oxygen concentration. Therefore, progressive anoxemia, which could be measured, was employed as the method of producing a burden on the cardiorespiratory system. To accomplish this, atmospheric air was used in a rebreathing apparatus fitted with a CO₂ filter and progressive anoxemia was produced by the patient's utilization of the oxygen in this system.

METHOD

The patient was prepared for the test in the manner used when a basal metabolic rate is taken. A calibrated McKesson spirometer with a specially constructed flowmeter was employed. All tests were started with ten liters of air in the spirometer. In order to prolong the test a continuous flow of 50 c.c. of oxygen per minute was allowed to filter into the system, care being taken to place the oxygen inlet at the opposite side of the tank from the air outlet. The spirometer was fitted with a

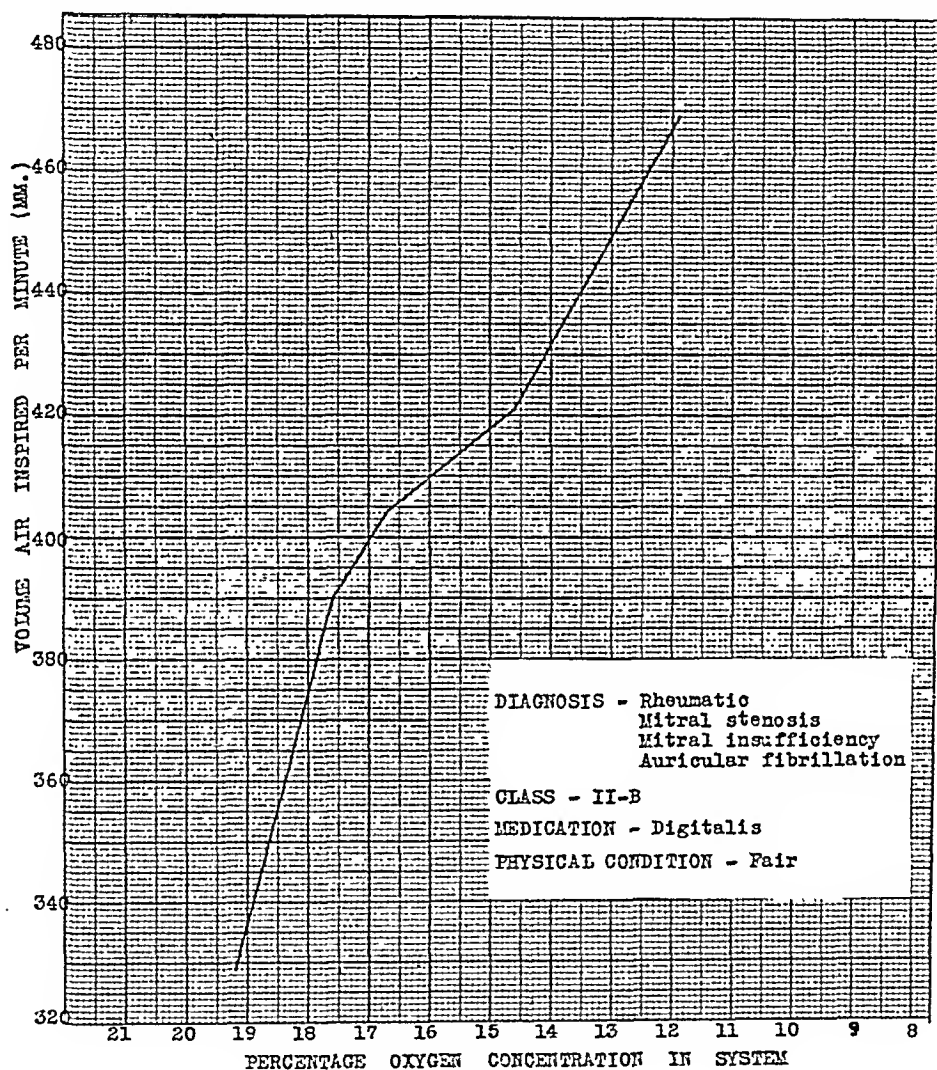


Fig. 4.—H. W., aged thirty-one years (cardiac).

double speed motor which spread out the graph and allowed for more accurate measurements. In all, forty normal and forty cardiac patients, including Class I, Class II-A, and Class II-B types, were tested several times. Representative results are graphically illustrated in the accompanying charts.

DISCUSSION AND RESULTS

It will be noted from the graphs that in the normal patient there is a definite decrease in the amount of air respired between the range of 16 per cent to 13 per cent, and about 12 per cent to 11.5 per cent oxy-

gen concentration, yet oxygen depletion of the system continues. From previously quoted work it will be noted that it is in this range that the cardiac output increases. The charts of the cardiac patients do not show this decrease in volume respiration. The cardiac group in Class I tend to show a leveling off in the 16 per cent to 13 per cent oxygen range but in no instance did a downward slope in the curve occur. The other cardiac patients in Class II-A and Class II-B, respectively, show either a curve which has a slight tendency to level off or a continued sustained elevation in the curve of the graph.

From our observations it appears that at certain stages the respiratory system must function with a facility inversely proportional to the ability of the heart to increase its load. At present we are unable to state the attending chemical changes occurring in the body during this procedure. There is the definite possibility that these curves may lend themselves to corrections for surface area and individual minute oxygen consumption, but we have reason to believe that these corrections are immaterial. We feel that this method takes into account important factors, not given adequate consideration in the past. Furthermore, it eliminates the variables inherent in the previous methods.

CONCLUSIONS

1. Normal individuals respond to anoxemia differently from cardiac patients.
2. The difference consists in the ability of the heart to compensate for the burden produced by anoxemia.
3. The burden placed on the cardiorespiratory system can be quantitated.
4. The curve of response to the burden seems likewise to be quantitative.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING THE INHALATION OF TOBACCO SMOKE*

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IT HAS long been known that tobacco or nicotine may cause changes in cardiac activity. Traube,¹ in 1862, while studying the action of nicotine on the dog's heart observed that there is at first a slowing or even temporary cardiac arrest followed by tachycardia with reinforced contractions. Since that time there have been a great many experiments showing that tobacco or nicotine may alter cardiac activity and may provoke various auricular and ventricular arrhythmias and auriculoventricular block of all grades.

Bull, Clere, and Pezzi,² in 1914, were among the first to use the electrocardiograph in studying the effects of nicotine on the heart. They took electrocardiograms on dogs and rabbits which had been injected with toxic doses of nicotine and observed nodal rhythm, auricular flutter, and heart-block. These observations have been repeatedly confirmed and recently extended by Mattioli³ who studied the electrocardiographic changes in rabbits following acute and chronic tobacco poisoning and acute nicotine poisoning; the changes were similar in all experiments and consisted chiefly of partial heart-block, increase in amplitude of the T-waves, and decrease in amplitude of the R-waves.

Ssalisehtsheff and Tschernogoroff^{4, 5} were the first to study the effect of the inhalation of tobacco smoke on the human electrocardiogram. They asked healthy individuals to smoke until toxic symptoms appeared and electrocardiograms were taken every five to ten minutes during the test. Arrhythmias and heart-block were not observed and characteristic alterations in the form and amplitude of the several waves were not found save in two instances where there was slight lowering of the T-waves. The heart rate was accelerated in each instance save one where the rate slowed from 75 to 52 a minute.

Our interest in the effect of tobacco on the electrocardiogram was stimulated by observations on a healthy young man of eighteen years who complained of dizziness on smoking. Electrocardiograms taken after the inhalation of tobacco smoke showed well marked inversion of the T-waves in Leads II and III while at other times the T-waves were upright and of normal amplitude. To determine whether or not this is a common phenomenon similar tests have been carried out on 45 individuals.

*Presented in brief before the New England Heart Association, Massachusetts General Hospital, Boston, Nov. 9, 1936.

Method.—The subject to be tested was asked not to smoke for at least one hour preceding the test. After resting comfortably in a chair or bed until the blood pressure and pulse rate reached steady values a control electrocardiogram was taken. The smoke of a cigarette was then inhaled until either toxic symptoms appeared or the cigarette was finished. Electrocardiograms, and blood pressure and pulse rate determinations were taken repeatedly and notes were made of significant signs and symptoms. In order to allow comparison between the several tracings standardization of the electrocardiograms was carefully done and care was taken that the subject did not shift the position of the body during the course of the experiment. The procedure varied somewhat in that occasionally a pipe or cigar was smoked rather than a cigarette, and sometimes two or three cigarettes were smoked consecutively. In some instances cubes were smoked as a control and sometimes the effect of atropine was noted.

Data.—Among the 45 subjects tested there were 3 women. The ages of individuals in the group varied between eighteen and sixty-four years. Four were nonsmokers, 4 smoked occasionally, and 37 were confirmed tobacco addicts. Sixteen gave a history of symptoms on smoking, chiefly dizziness, palpitation, and nausea. Two had hypertensive, 8 coronary, and 1 hypertensive and coronary heart disease. During the test 28 complained of cerebral, cardiac, or gastrointestinal symptoms.

The temporary increases in heart rate and in blood pressure following the use of tobacco are well known. Thirty-nine of the 45 showed an increase in heart rate which averaged 13 a minute, 4 a decrease which averaged 15, and 2 no change. Twenty-four of 31 tested exhibited an increase in arterial blood pressure which averaged 13 mm. Hg systolic and 7 mm. diastolic; 6 showed a decrease averaging 13 mm. systolic and 3 mm. diastolic; 1 showed no change.

Twenty of the 45 tested showed significant electrocardiographic changes other than variation in heart rate. Of the 20, 2 were nonsmokers, 1 smoked occasionally, and 17 were heavy smokers; 10 of the 20 gave a history of symptoms on smoking and 15 had symptoms while the test was being done.

The commonest electrocardiographic change was a decrease of from 1 to 4.5 mm. in amplitude of the T-waves in Lead I or II which was observed in 15 instances. In two instances there was an increase in the amplitude of T in Lead I or II. A slight decrease in the length of the P-R interval was observed twice, both times associated with fast heart rates. In two instances the P-R interval was increased, once from 0.16 second to 0.22 second. There was a decrease of 20 per cent or more in the amplitude of the QRS complexes in 4 instances and an increase in one other.

The T-wave changes are of especial interest. Fig. 1 shows electrocardiograms taken on a healthy young man aged eighteen years who

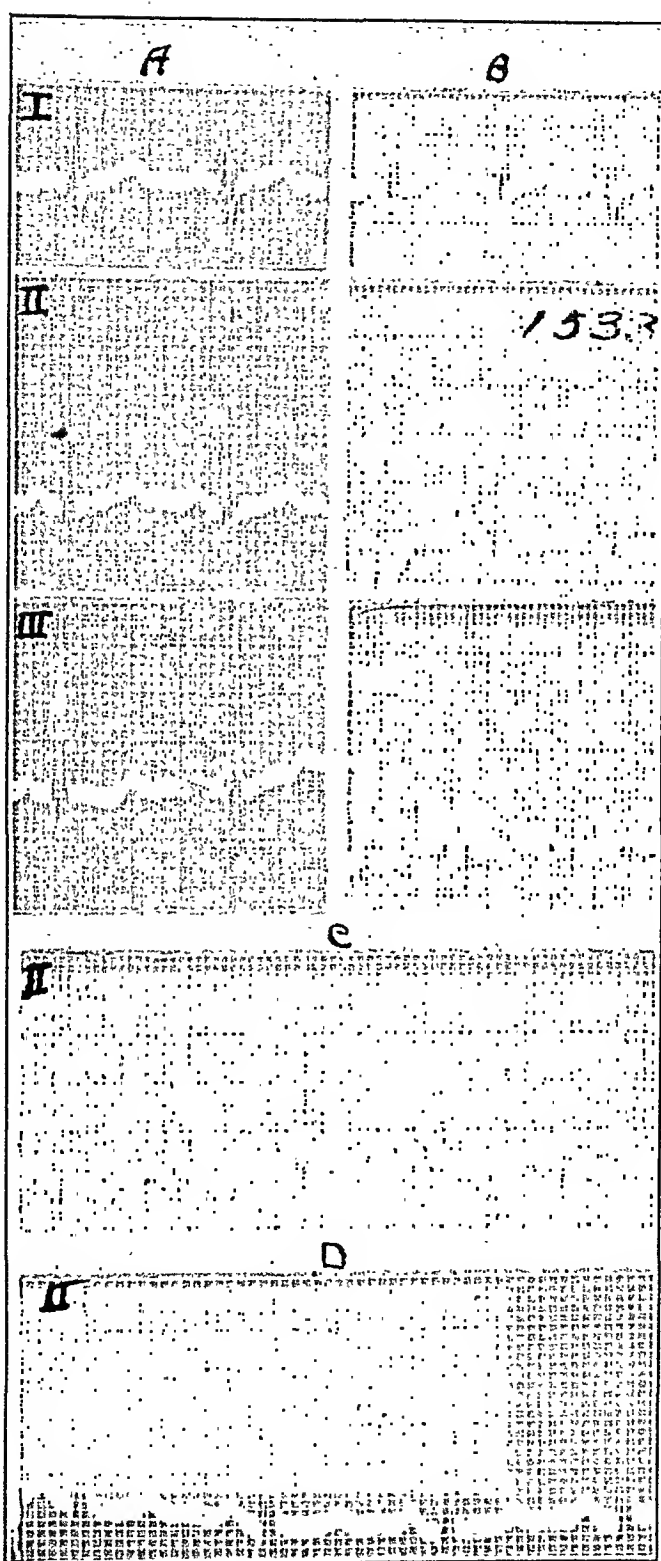


Fig. 1.—Electrocardiograms taken on a healthy young man, aged eighteen years. A, control; heart rate 85. B, immediately after smoking; rate about 100. C, Lead II taken thirty seconds after B; rate about 100. The Q-wave is more prominent in this strip but there is no doubt that it is Lead II. D, Lead II (a continuation of C) taken one minute later.

complained of dizziness on smoking cigarettes. *A* is the control and *B* the electrocardiogram taken immediately after smoking; note the decrease in the height of T in Leads II and III. *C* is a strip of Lead II taken about thirty seconds after *B*; note the well-marked inversion of T. *D* was taken a minute later; the T-waves are again upright. The test was repeated on another occasion with similar results. Unfortunately the subject was not available for further tests.

The electrocardiograms in Fig. 2 were taken on a healthy woman aged twenty-six years. *A* is the control and *B* the electrocardiogram taken after she finished smoking a cigarette. She complained of dizziness and slight nausea. There is marked lowering of the T-waves in Leads I and II, decrease in amplitude of the QRS complexes, increase in prominence

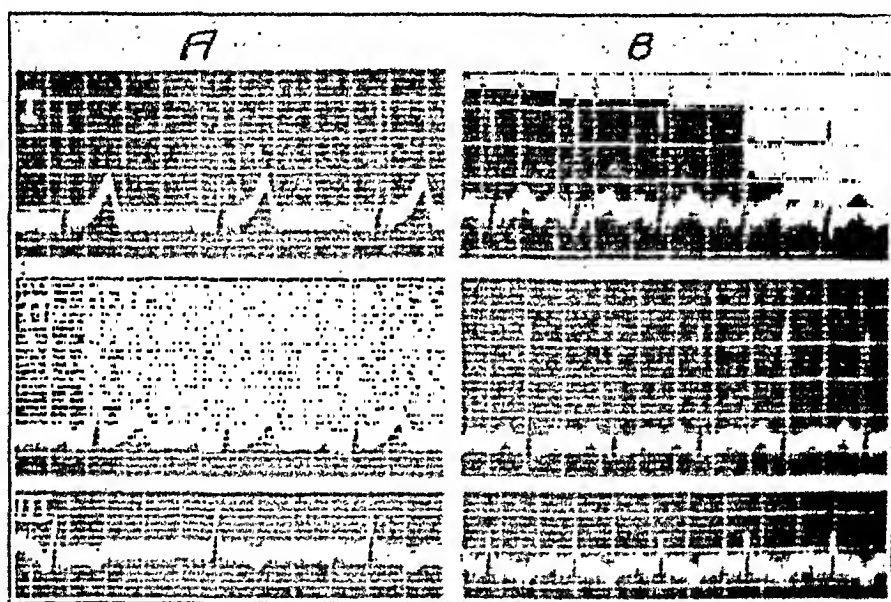


Fig. 2.—Electrocardiograms from a healthy woman, aged twenty-six years. *A*, control; heart rate 89, blood pressure 119/75. *B*, after smoking; heart rate 130; blood pressure 120/90.

of the P-waves, and a slight decrease in the P-R interval. The electrocardiograms in Fig. 3 were taken on the same individual. *A* is the control tracing. *B* was taken ten minutes after 0.002 gm. of atropine sulfate was given intravenously; note especially the decrease in the height of the T-waves in Leads I and II. *C* was taken immediately after the inhalation of cigarette smoke and ten minutes after *B*; the amplitude of the T-waves in Lead II has increased. *D* was taken two minutes after *C*; the T-waves are now comparable to those in *B*.

The electrocardiograms in Fig. 4 were taken in the case of a healthy woman aged twenty-four years. *A* is the control electrocardiogram, *B* was taken after the smoking of one cigarette, and *C* after the smoking of a second cigarette. At this time she was pale, and complained of slight dizziness. Note the decrease in amplitude of the T-waves in all

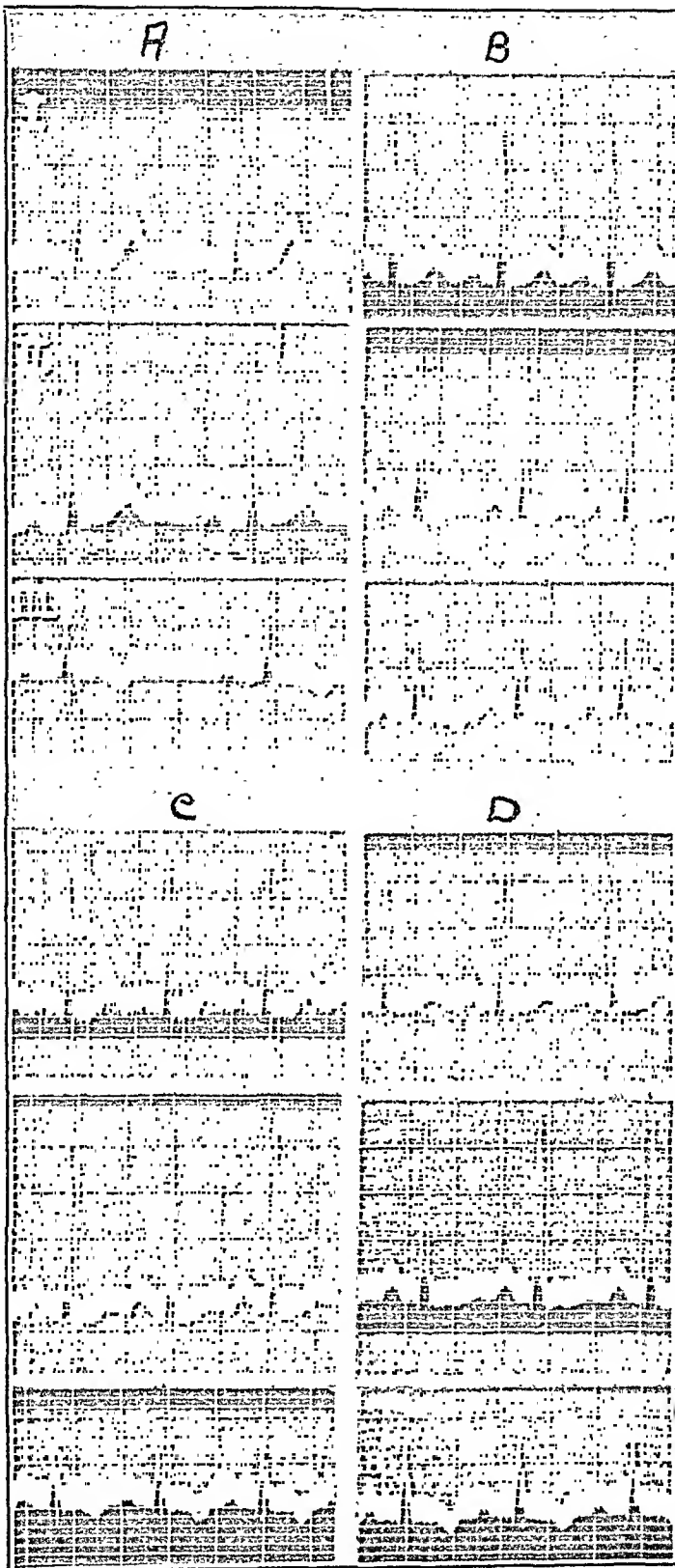


Fig. 3.—Electrocardiograms from a woman, aged twenty-six years. A, control; heart rate 85, blood pressure 120/75. B, after 0.002 gm. atropine intravenously; rate 130; blood pressure 120/90. C, taken immediately after smoking; rate 130, blood pressure 120/95. D, taken two minutes later; rate 125, blood pressure 110/85.

leads. *D* was taken four minutes after *C*. The electrocardiograms in Fig. 5 were taken on the same individual. *A* is the control and *B* was taken two minutes after the intravenous injection of 0.002 gm. atropine

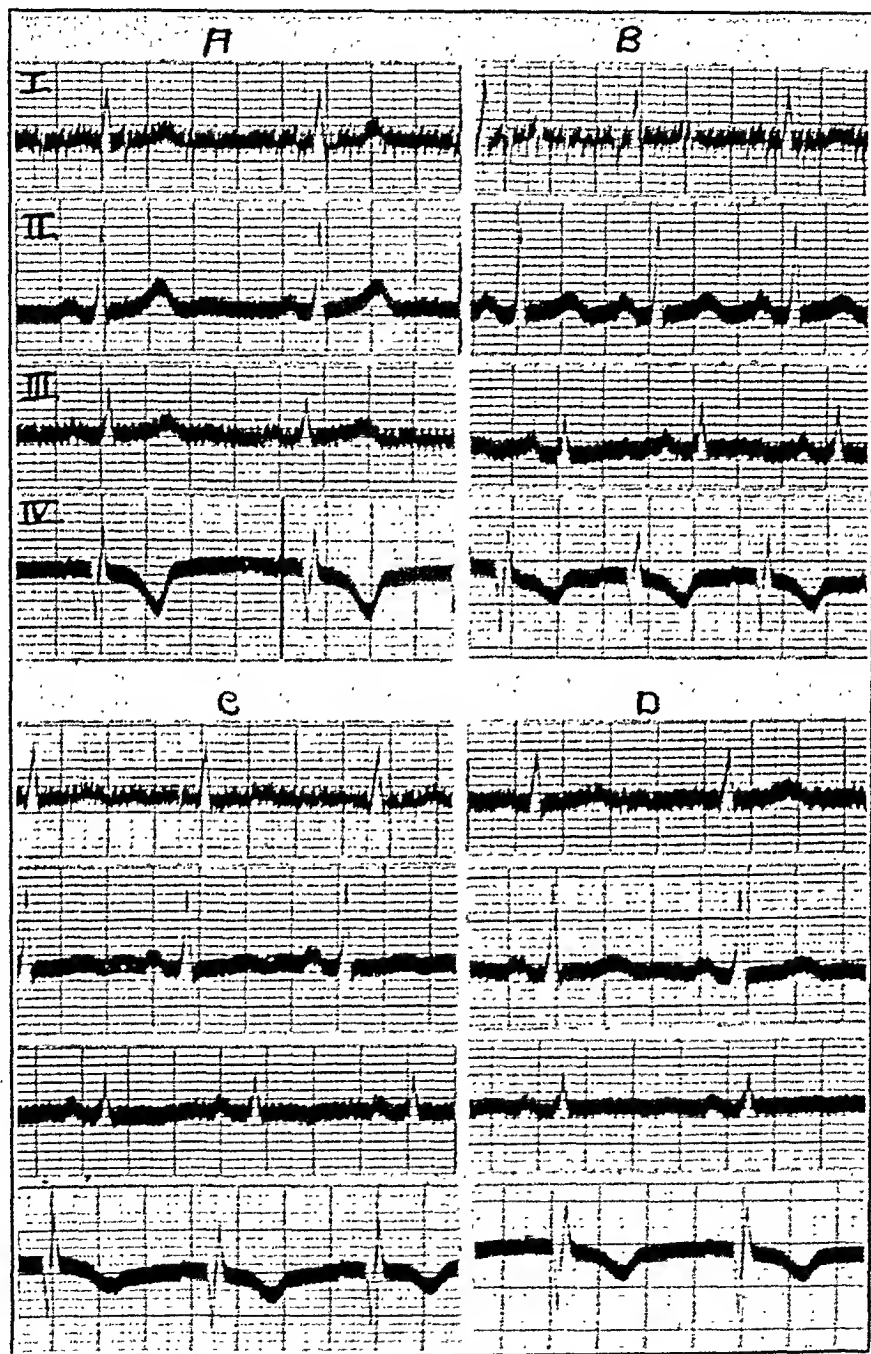


Fig. 4.—Electrocardiograms from a woman, aged twenty-four years. *A*, control; heart rate 65, blood pressure 100/70. *B*, after one cigarette; rate 90, blood pressure 125/85. *C*, after a second cigarette; rate 85 to 90. *D* was taken four minutes after *C*; rate 75, blood pressure 110/79. (Lead IV was taken with the electrode from the right arm placed on the chest.)

sulfate. *C* was taken two and *D* forty-six minutes later. Note especially the flattening of the T-waves in *C*.

Six individuals were tested with adequate doses of atropine as well as with tobacco smoke. In two individuals neither atropine nor tobacco caused a significant change in the T-waves, in two others both drugs caused a moderate decrease in the amplitude of the T-waves and in the

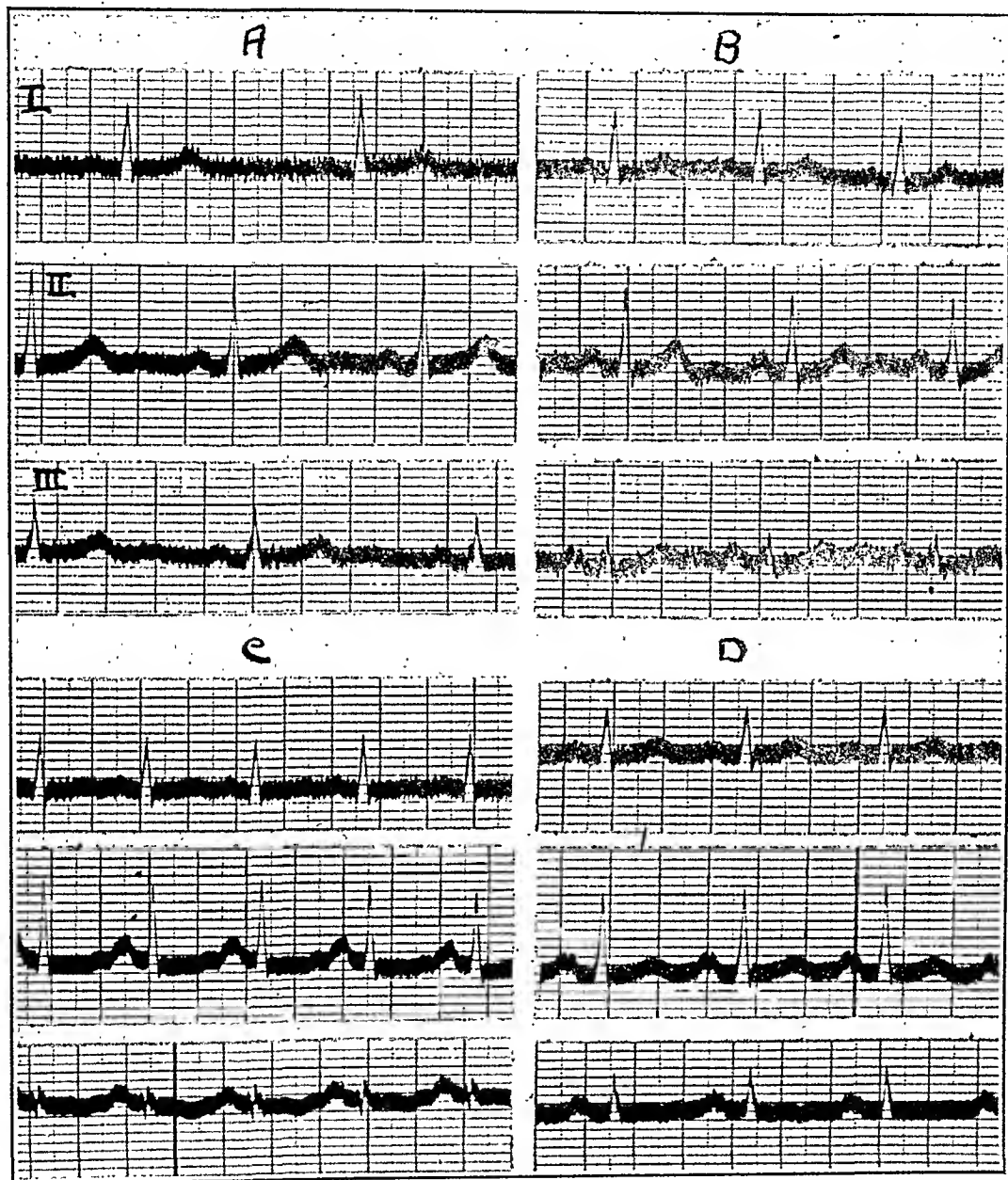


Fig. 5.—Electrocardiograms from a woman, aged twenty-four years. *A*, control; heart rate 65, blood pressure 100/72. *B*, taken two minutes after 0.002 gm. atropine; rate 90. *C*, four minutes after atropine; rate 130, blood pressure 102/78. *D*, forty-six minutes after atropine, rate 105.

remaining two, both drugs caused a marked lowering of the T-waves. Thus in each instance the effects of atropine and of smoking on the T-waves were similar.

DISCUSSION

It is interesting to consider how the inhalation of tobacco smoke might influence the electrocardiogram.

When tobacco is smoked the chief poisons carried over are pyridine bases, carbon monoxide, and nicotine. The pyridine compounds are irritating to the mucous surfaces but the amounts absorbed are too small to be of toxicological interest.

A carbon monoxide saturation of the hemoglobin as high as 8 per cent has been shown to occur after smoking but usually the saturation is not over 3 or 4 per cent. It is extremely unlikely that this amount is ordinarily injurious, as the healthy individual does not, in most cases, exhibit symptoms until the hemoglobin saturation reaches 15 to 20 per cent. Exceptionally an individual may be extremely sensitive to this gas and notices mild symptoms with concentrations such as may result from smoking. Although it has been shown that significant inversion of the T-waves of the electrocardiogram may result from carbon monoxide poisoning this is highly unlikely under the circumstances considered here.

The poison most seriously to be considered is nicotine. The cigarette chiefly used in these tests contains about one gram of tobacco which, analysis has shown, yields 2.52 per cent nicotine. The smoke from about two-thirds of the cigarette may be inhaled if allowance is made for the stump and the amount burned with the cigarette out of the mouth. If the cigarette is smoked in a period of five minutes, at least one-half of the nicotine will carry over in the smoke and of this at least one-fourth will be absorbed into the system. Consequently somewhere in the neighborhood of 2.0 mg. of nicotine will be taken into the circulation. This amount is sufficient to produce its characteristic action which is stimulation of the entire nervous system followed by depression.

The chief effects upon the heart and vessels of stimulation or paralysis of the vagus and sympathetic nerves are well known. The action of nicotine on these nerves or their ganglia offers an adequate explanation for the changes in pulse rate and blood pressures observed during smoking. Whether or not the same explanation holds true for the T-wave changes is problematical. Many observers have shown that stimulation of the sympathetic nerves or the injection of adrenin causes an increase in amplitude of the T-waves while stimulation of the vagus nerves or the injection of acetylcholine causes a decrease in their amplitude. In man, paralysis of the vagus nerves with atropine is usually regarded as having little or no effect on the T-waves.

In a susceptible individual the initial lowering of the T-waves occurs during the inhalation of the tobacco smoke but the maximum lowering or even inversion of T occurs shortly after smoking ends. The inversion or flattening of T lasts only a few minutes and within half an hour the T-waves assume their normal form and amplitude. If a second cigarette is smoked while the T-waves are still flattened as a result of the first, the T-waves may temporarily increase in amplitude due presumably to sympathetic stimulation. This increase in amplitude

is quickly followed by a decrease and the T-waves may become lower than before. This temporary increase in T may also be seen (Fig. 3) when a cigarette is smoked during full atropinization which has flattened the T-waves. Here again it is probably due to sympathetic stimulation. We were surprised to find that the T-wave changes after full atropinization and after smoking were strikingly similar. Actually the

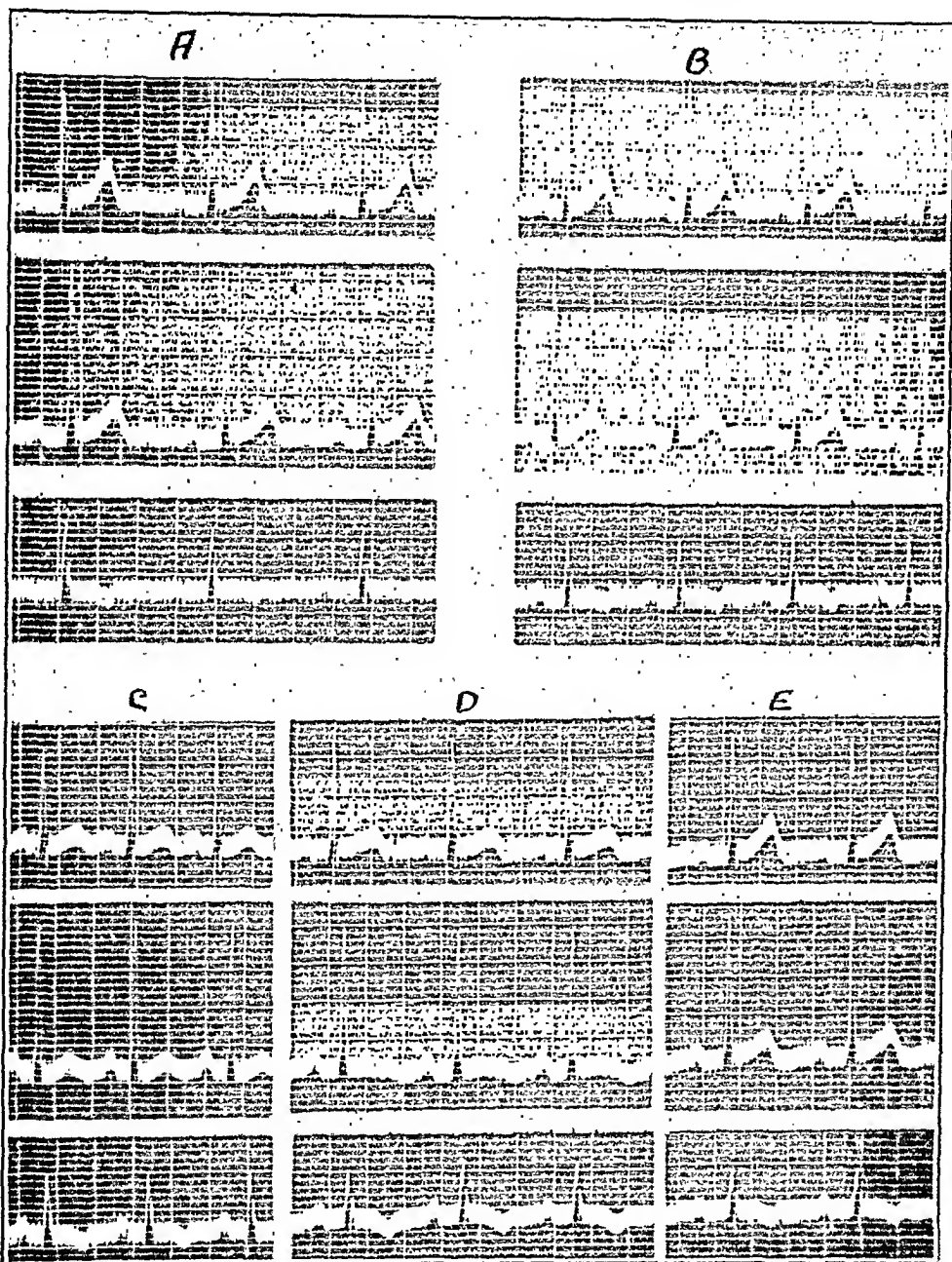


Fig. 6.—Electrocardiograms in the case of a healthy woman, aged twenty-six years. *A*, control; heart rate 80. *B*, taken twenty-three minutes after 1.3 mg. atropine, subcutaneously, rate 92. *C*, taken during smoking; rate about 120. *D*, taken eight minutes after smoking; rate about 100. *E*, taken thirty-six minutes after smoking.

effect of one drug may be used to predict the effect of the other. The individuals showing marked lowering or inversion of the T-waves with tobacco and with atropine were in each instance young and healthy but emotionally labile. More stolid individuals, even those with severe coronary arteriosclerotic heart disease did not show these T changes.

It is interesting that Cohn, Fraser, and Jamieson,⁶ who found that atropine alone produced no effect on the T-waves, did find that this drug brought on or intensified the characteristic modification (lowering or inversion) of the T-waves seen during digitalization. White and Sattler⁷ and Favill and White⁸ also observed that atropine increased the digitalis effect on the T-wave while exercise had the opposite effect. We have observed this same synergistic effect with atropine and nicotine in susceptible individuals but only when atropine was given in amounts insufficient to produce its characteristic effect alone (Fig. 6).

Undoubtedly a few individuals are peculiarly susceptible to the small amounts of nicotine absorbed during smoking. So far as the cardiac effects of this amount of nicotine are concerned its action suggests chiefly parasympathetic paralysis and sympathetic stimulation. Some proof that parasympathetic paralysis may account for the flattening or inversion of the T-waves is afforded by the similar flattening following atropine. Both drugs cause an increase in heart rate but no lowering of blood pressure.

Although it is possible that nicotine may cause the T-wave changes by its action on the heart muscle fibers, there is no reason to believe that myocardial ischemia is a factor. These changes occurred most strikingly in young healthy individuals, anginal pain was never present during the tests, and amyl nitrite failed to influence the T-wave changes following both nicotine and atropine. Furthermore, Laubry and his co-workers⁹ have shown that tobacco or nicotine in small amounts actually increases the coronary flow in the isolated rabbit's heart and that toxic doses are necessary to produce vasoconstriction.

There have been reported and we have observed,* attacks of angina pectoris following smoking in patients with small coronary reserve. The explanation commonly offered is that the attacks are the result of coronary vasoconstriction. However, the true explanation, in some instances at least and probably in most, is the sudden increase in work of the heart. This is shown by a striking increase in heart rate, or blood pressure or both. It is this extra work suddenly placed on the heart that is responsible for the precipitation or aggravation of angina pectoris in patients with little heart reserve and unusual sensitivity to tobacco smoke.

SUMMARY AND CONCLUSIONS

1. We have made observations on 45 individuals of varying ages, some with heart disease, during the inhalation of tobacco smoke.
2. It has long been known that tobacco or nicotine may be responsible for temporary symptoms referable not only to the cardiovascular system but other systems as well. Thirty-nine of the 45 patients in this series

*These observations will be reported later in detail.

exhibited on smoking an increase in heart rate which averaged 13 a minute; 24 of 31 tested showed an increase in arterial blood pressure which averaged 13 mm. Hg systolic and 7 mm. diastolic.

3. Of particular interest were certain electrocardiographic changes, especially lowering or inversion of the T-waves, which occurred during the test in 15 individuals.

4. The probable explanation for the T-wave changes lies in the characteristic action of nicotine on the cardiac ganglia. Actually the T-wave changes following smoking were found to be similar to those following atropinization.

5. It is suggested that in those occasional instances where attacks of angina pectoris are precipitated by smoking ("tobacco angina") the attacks are not the result of coronary vasoconstriction but the result of a sudden increase in the work of the heart as shown by the increase in blood pressure, or heart rate or both.

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ELECTRICAL ALTERNANS OCCURRING IN A CASE WITH PERICARDIAL EFFUSION*

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ELECTRICAL alternans consists of a regular alternation at equal intervals in amplitude or contour, or both, of various phases of the electrocardiographic tracing. In frequency, it is in sharp contrast to the usual and well-known type of alternans which is confined to the pulse or apex beat, but not registered on the electrocardiogram. Electrical alternans, like pulsus alternans, is a sign of reduced myocardial power, yet the electrocardiogram only rarely demonstrates it.¹ In a series of 6,000 electrocardiograms at the Cardiac Clinic of the University of Illinois, not one instance of electrical alternans was encountered.

The most frequent forms are those involving the T alone or both the QRS and T-waves, while alternation of the P-waves alone is one of the rarest forms as described by Chini.² Alternation in the auriculoventricular and intraventricular conduction in man has recently been observed.^{3, 4} Electrical alternans may vary in degree; it may be continuous, but more often is transient,^{4, 5} a fact which may account for its rarity. It is of less significance when seen in extreme tachycardia⁶ or following premature contractions.⁷

Mines⁸ in 1913 was first to describe isolated electrical alternans in the electrocardiogram obtained from the frog's heart. A number of papers dealing with the experimental and the clinical side of electrical alternans have followed, especially in the foreign literature: Condorelli,⁹ Galata,¹⁰ Pezzi¹¹ and Chini¹² have called attention to this phenomenon during the last decade. Bruno Kisch¹³ considers alternation as an expression of the mechanical behavior of the ventricles. He believes that all types of alternans are expressions of a basic alternans of the heart, "herzalternans." According to him, this phenomenon may in various instances be demonstrated best by the electrocardiogram, by the pulse curve, or by other methods of examination. Katz¹⁴ states, "We feel that electrical alternans has the same significance, at a slow rate particularly, as pulsus alternans."

Hamburger, Katz, and Saphir⁴ were the first in this country to describe two cases of electrical alternans without pulsus alternans. In the experience of these authors, the combination of mechanical and electrical alternans is rare, while isolated electrical alternans without apparent

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mechanical alternation they considered most unusual. In one case the alternans was a discordant one of the QRS and T-waves. In the second the alternation involved the QRS only. They also cite a case, displaying alternation of the auriculoventricular conduction only. In their first case autopsy revealed an anomalous distribution of the right coronary artery, narrowing of the mouth of this artery, generalized coronary sclerosis, and multiple microscopic myocardial infarcts. In the second case, multiple minute carcinomatous metastases within the myocardium and in the blood vessels of the heart were found post mortem. They concluded that malnourishment of fractions of the heart was responsible for the electrical alternation.

Missal and CRAIN² recently reported a case with bundle-branch block displaying alternation in the intraventricular conduction and T-waves. There were cycles showing a decrease of the width of the QRS from 0.13-0.10, followed by T-waves which became inverted. This phenomenon was observed in the absence of premature contractions, and respiratory excursion did not have any relationship to this unique alternation. They suspected the patient's hyperactive carotid sinus to be causal, although at no time did they succeed in producing this alternation by stimulating the carotid sinus, even to the point of convulsions.

Brody and Rossman⁵ just recently have reported two additional cases of electrical alternans, one with pulsus alternans and one without. The first case suffered from degenerative heart disease. The alternation involved the QRS deflections only and was transient. An arteriogram taken at the time when the alternans was absent, showed no mechanical alternation. The second case had rheumatic heart disease and was thirty-nine years old. The alternans was confined to the QRS complexes. She subsequently developed auricular fibrillation.

Another case of electrical alternans with autopsy findings is added to the literature, occurring in a patient with pericardial effusion, resulting from carcinomatous metastasis to the pericardium. The electrocardiogram was encountered after the patient's death, hence the absence of a clinical study of the pulse for mechanical alternation.

REPORT OF CASE

Mrs. G., fifty-four years of age, married, and a housewife, was admitted to the orthopedic service of the Mount Sinai Hospital on April 19, 1936. Three months before admission she began to suffer from "arthritic" pains afflicting her spine, shoulders, and hips. She also knew of an existing hypertension which was symptomless, except for an occasional dizzy spell. Three weeks before entry, while undergoing hot pack treatment for her "arthritis," she suddenly became dyspneic, experiencing substernal pressure, but no actual pain. Since that time, besides pains around and in the joints, she had had substernal discomfort, with choking sensation when lying down. There was some cough, which at times would cause slight pain in the left axilla. There had been some loss of weight in the last four months.

Her previous history revealed the removal of the left ovary and tumor of breast, ten and eight years ago respectively. There had been multiple pregnancies.

The medical consultant found a fairly obese woman, face pale, who could not lie down. Her temperature was 99.8° F.; pulse, 120 and regular; and blood pressure, 148/100. The veins of the neck were not distended. The heart extended about 13 cm. to the left and 4 cm. to the right of the midsternal line. There was appreciable retromanubrial dullness. The heart sounds were clear, but distant. No rubs were heard and there was evidence of fluid in the left pleural cavity,

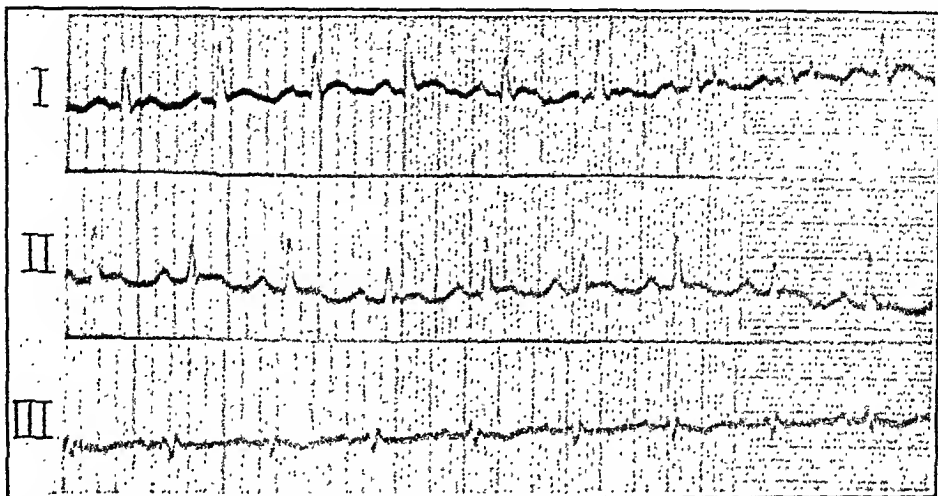


Fig. 1.—Electrical alternans in all three leads involving the QRS complexes. In Lead I the P-R interval in certain cycles is slightly prolonged, concordant with the QRS alternation. S-T₁ and S-T₂ are elevated and convex. Rate 120. Record taken April 20, 1936.



Fig. 2.—A 2:1 auricular flutter is present with a ventricular rate of 150. No electrical alternation in Lead I, but the QRS complexes are all low. In Lead II, there is transient electrical alternation, the high complexes being not quite as high, and the lower not quite as low as in the corresponding lead of Fig. 1. Record taken April 25, 1936.

with obliteration of Traube's space. The liver was not felt. There was no edema of back or extremities. There was no leucocytosis, the urine was not abnormal, and the Kahn test and routine blood chemistry showed no abnormalities.

Because of the distant heart sounds a bedside film was taken. It revealed a markedly dilated and hypertrophied heart, the enlargement being mostly in the region of the left ventricle, fluid in the left pleural cavity, and a slight amount of fluid in

the right pleural cavity. The configuration of the heart was such that neither the roentgenologist nor the consultant did as much as suspect fluid in the pericardium.

An electrocardiogram at this time (Fig. 1) showed upward convexity of the S-T segment in Leads I and II, and frank continuous electrical alternans of the QRS complexes in all leads. In Lead I the P-R interval of certain cycles was slightly prolonged concordant with the QRS alternation. Another electrocardiogram (Fig. 2) four days later showed a definite 2:1 flutter with a ventricular rate of 150 per minute, and absence of the alternans in Lead I, but the QRS complexes were all low. In Lead II there was a transient electrical alternans, the higher complexes being not quite as high and the lower complexes not quite as low as in the corresponding lead of Fig. 1.

The patient became rapidly worse and died nine days after admission. Necropsy by Dr. Israel Davidsohn revealed metastatic adenocarcinoma to the lungs, mediastinal glands, mediastinal pleura, and the pericardium. The pericardium contained 1,000 c.c. of a bloody fluid. The heart weighed 358 grams, the wall of the left ventricle measuring 14 mm. Grossly there was no evidence of infarction, fibrosis, or metastases. Both auricles were normal in size, and showed no evidence of metastases, special attention being paid to the region of the S-A node. The coronary arteries showed no abnormalities. The liver and kidneys showed a few metastatic nodules. The uterus, left adnexa, and right tube were absent and the right ovary was normal. The right breast presented an old scar.

Microscopic examination of the heart revealed slight increases in the interstitial connective tissue. In the subepicardial layers accumulations of lymphocytes and plasma cells were present. The pericardium was markedly thickened by loose, young granulation tissue which was infiltrated with a large accumulation of lymphocytes and plasma cells. In some areas large atypical epithelial cells were seen which had hyperchromatic nuclei and were similar to those seen in the tumor of the lung. Tissue examination for tuberculosis and guinea pig inoculation gave negative results. While the source of the metastatic carcinoma was not found, it was the opinion of the pathologist that it may have originated in the ovary or in the tumor of the breast that were removed some years previously in another hospital.

COMMENT

The absence of the electrical alternans from Lead I of the second electrocardiogram (Fig. 2) does not necessarily indicate that the condition of the heart has improved, as it might appear at first thought. It is more likely, according to Hamburger and his associates,⁴ that its disappearance has exactly the opposite significance. Alternans means that at a certain stage of heart weakness certain portions are unable to respond normally to every stimulus but fluctuate alternately between a better and poorer or even no response. As the myocardial weakness progresses the condition is changed and the heart may give a poor but constant response to every stimulus.^{1, 4} This probably accounts for the constantly low QRS complexes in this lead. It is highly probable that the onset of the auricular flutter caused additional fatigue in an already embarrassed heart. On the other hand the reappearance of transient alternation in Lead II of this electrocardiogram may, paradoxically, indicate improvement of certain regions. However, that the heart is not

as strong as in the preflutter stage (Fig. 1) is indicated by the fact that the highest QRS complexes are not quite as high as those in the corresponding lead of the first electrocardiogram.

Since autopsy failed to elicit disease of the coronary arteries, extensive myocardial fibrosis, or metastatic lesions to the heart, the massive pericardial effusion is probably the cause of the electrical alternans in this case. It is not certain whether it is an isolated alternans or not, since the patient's pulse was not studied by an arteriogram. However, the patient's son, a well-trained physician who was in constant attendance gave the assurance of not having found a pulsus alternans by palpation or blood pressure determination.

That pericardial effusion may alter the voltage of the electrocardiogram is not unknown. Oppenheimer and Mann¹⁵ and Gager¹⁶ have described such changes. Scott, Feil, and Katz¹⁷ produced among other electrocardiographic changes, lowered voltage in their experimental pericardial effusion. Harvey and Whitehill¹⁸ found low voltage in eleven out of fifteen cases of pericardial effusion. They all attributed the change to the fluid which by its hydrostatic pressure caused anoxemia of the heart muscle. It was usual for the height of the deflections to increase, as the fluid was withdrawn, and the patient improved.

But that pericardial effusion may cause electrical alternans with or without pulsus alternans is not frankly recorded except for the remark by Harvey and Whitehill,¹⁸ "Alternation in amplitude was occasionally observed, as were changes in the form of each second or third complex. These changes were present only in fairly large effusions."

The essential disturbance in electrical, as well as in mechanical alternans, is alternation in the physiological response of parts of the heart due to fatigue or malnourishment of certain fractions of the myocardium. Coronary disease has been found in almost all of the cases reported. The literature contains many references to the so-called coronary alternans. Lewis¹⁹ was the first to demonstrate alternans of the heart following coronary occlusion. Condorelli²⁰ described electrical and pulsus alternans in man with disturbed coronary circulation, and also in dogs following coronary occlusion. Kisch¹³ found that interference with the nutrition of the dog's heart through coronary closure may cause alternation, even when the pulse does not increase. The alternation promptly disappeared following the removal of the coronary ligature.

Now, it has been assumed during the last seven or eight years that pericardial effusion may interfere with the coronary circulation. This assumption was employed to explain the changes in the S-T segment and T-wave often seen in pericardial effusion, clinical and experimental.^{16, 17, 21, 22} Katz and his associates²¹ thought that the hydrostatic pressure within the pericardium caused a "herztamponade," and thus

compressed the vascular channels, leading to anoxemia. The removal of the fluid in their experimental animals restored the electrocardiogram to the normal.

Hence, it is easily conceivable that the anoxemia thus produced may, under certain circumstances, interfere with the intrinsic circulation of certain regions of the heart muscle and thus lead to alternation. The slight fibrosis and subepicardial infiltration in this case were in all probability noncontributory; the former being inconspicuous and the latter only localized. The effect of the hydrostatic pressure may vary widely, depending upon rapidity of filling, amount of fluid, and distensibility of the sac, according to Katz.²¹ The electrical alternans then in this case with pericardial effusion was presumably caused by anoxemia and may be designated as the coronary type of Kisch, although the coronaries were structurally normal.

The auricular flutter developing a few days before death in the absence of metastasis to the auricles, is additional evidence of an existing anoxemia. That pericardial effusion may cause disturbance in cardiac rhythm and conduction is known. Gager¹⁶ reported an instance of heart block that disappeared after the withdrawal of the fluid. Harvey and Whitehill¹⁸ found two cases of auricular fibrillation, one ceased spontaneously, and the other immediately following the withdrawal of 800 c.c. of fluid. In the experiment of Katz²¹ and his associates, arrhythmias were encountered which were abolished by removal of the fluid. Hence, the auricular flutter in this case is analogous to that seen in coronary disease—anoxemia being the essential cause in both instances.

SUMMARY

A case of electrical alternans occurring in a patient with pericardial effusion is added to the literature.

Autopsy revealed carcinomatous pericarditis with 1,000 c.c. of bloody fluid. The coronary arteries were patent and not abnormal, and the myocardium showed only slight fibrosis.

It seems very likely that the hydrostatic pressure within the pericardial sac compressed the vascular channels and caused an anoxemia. The latter is conceivably the cause for the alternation, which may be designated as the coronary type of Kisch in spite of structurally normal coronary arteries. Changes in the S-T segment, frequently occurring in pericardial effusion, were also present.

Auricular flutter appeared a few days before death. In the absence of metastasis to the auricles, this arrhythmia is attributed to the anoxemia—resulting from “herztamponade.”

Electrical alternans, like pulsus alternans, carries a grave prognostic significance.

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Special Article

STANDARDIZATION OF PRECORDIAL LEADS

JOINT RECOMMENDATIONS OF THE AMERICAN HEART ASSOCIATION AND THE CARDIAC SOCIETY OF GREAT BRITAIN AND IRELAND

In the last few years, electrocardiographic leads in which an electrode placed upon the precordium is paired with an electrode in contact with some part of the body distant from the heart have come into widespread use. The confusion which has resulted from the lack of uniformity and precision in the technique and nomenclature employed by different observers in connection with leads of this kind has led to an almost universal desire that a standard practice be established. To this end the American Heart Association and the Cardiac Society of Great Britain and Ireland have each appointed a committee to consider this matter and make recommendations. The two committees have conferred and have agreed jointly to make recommendations with reference to the routine use of a single precordial lead. It is understood that either committee may make additional reports with reference to multiple precordial leads and other matters not dealt with in the present report.

1. It is recommended that those who employ a single precordial lead place the precordial electrode upon the extreme outer border of the apex beat, as determined by palpation. If the apex beat cannot be located satisfactorily by palpation the electrode may be placed in the fifth intercostal space just outside the left border of cardiac dullness, or just outside the left midclavicular line if percussion of the heart is unsatisfactory. Where precordial leads are taken by a technical assistant, the position for the precordial electrode should be marked on the chest by the physician.

2. It is recommended that a single precordial lead in which the precordial electrode has the location specified in the preceding paragraph be known as Lead IV B when this electrode is paired with an electrode in the left interscapular region; Lead IV R when it is paired with an electrode on the right arm; Lead IV L when it is paired with an electrode on the left arm; Lead IV F when it is paired with an electrode on the left leg; and Lead IV T when it is paired with a central terminal connected through equal resistances of 5,000 or more ohms to electrodes on each of the three extremities mentioned.

It is suggested that for all ordinary purposes Lead IV R or Lead IV F be employed. The latter lead should have the preference until it has been established that the former, which is somewhat more convenient, is equivalent to the latter for all practical purposes, or yields results of equal value.

3. It is recommended that in taking the precordial leads specified the galvanometer connections be made in such a way that relative positivity of the apical electrode is represented in the finished curve by an upward deflection (a deflection above the isopotential level) and relative negativity of the apical electrode by a downward deflection.

It is urged that this convention be adhered to in the case of precordial leads other than those specified, and also in the case of all leads in which one electrode is placed much closer to the heart than the other. In other words, it shall be the standard convention in taking such leads to make the galvanometer connections in such a way that relative positivity of the electrode nearer the heart is represented by an upward deflection.

4. It is recommended that with the galvanometer connections made as described in the preceding paragraph, the deflections of precordial leads be designated by the symbols P, Q, R, S, and T, and that in the application of these symbols the same conventions be employed as in the case of the standard limb leads.

5. It is recommended that in taking precordial leads the electrocardiograph be so adjusted that a deflection of one centimeter in the finished record corresponds to a potential difference of one millivolt as in the case of the standard limb leads. Any reduction in sensitivity made necessary by very large deflections should be clearly indicated on the curve preferably by photographing the effect of introducing a potential difference of one millivolt into the galvanometer circuit.

6. It is recommended that the greatest dimension of the apical electrode employed in taking the leads specified in this report be 3 cm. or less. A circular electrode between 2 cm. and 3 cm. in diameter should ordinarily be employed.

7. It is recommended that the terms Lead IV (R, F, etc.); apical lead, apex-leg lead, etc., be used henceforth only in connection with the leads specified in this report.

Signed

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BRUCELLA MELITENSIS BACTEREMIA ASSOCIATED WITH VEGETATIVE ENDOCARDITIS*

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THERE is an impressive rarity of references in the literature to cases of endocarditis due to *Brucella melitensis*. In 1928, Scott and Saphir¹ reported one case and found only five additional references to cases of this nature. Since that time other single cases have been reported by Gate and Ravault,² De La Chapelle,³ Casanova and Ignazio,⁴ Gounelle and Warter,⁵ and Rennie and Young.⁶ De La Chapelle, in commenting on his case,³ states that, "A survey of the literature failed to discover any fatal cases with necropsy findings of subacute bacterial endocarditis due to *Br. melitensis* A. in this country." He is careful to point out that among the few cases which had been reported with autopsy findings up to the time of his report the vegetative endocarditis was implanted on an old deformed valve or superimposed upon chronic (rheumatic) endocarditis. In the few cases which have been reported since De La Chapelle's, a careful scrutiny of the findings seems to indicate that the presence of an old endocardial lesion is the rule. In the present case there was undoubtedly evidence of preceding chronic mitral involvement, probably rheumatic in origin.

REPORT OF CASE

J. S., a white male, fifty-four years of age, who had been a moulder for the past thirty years, entered the Grace Hospital on March 26, 1936. He complained of fever and chills. The past history included a very short attack of "malaria" at the age of nineteen. He had had a frostbite seven years before admission, and a fracture of the right clavicle shortly thereafter. The parents were both dead. The causes of death were unknown. There was no history of tuberculous contact. The patient had been having chills and fever for seven weeks before admission to the hospital. Early in this illness there had been a chill every day. The chills now occurred every second or third day, lasting from five to thirty minutes. There was complaint of marked weakness and lassitude. A review of the cardiorespiratory system revealed that there had been considerable coughing, productive in nature. The patient raised four to eight ounces of sputum daily. It had never been blood-streaked but was thin and watery. This cough had been present for four weeks prior to admission. There was no hemoptysis or epistaxis. There had been hoarseness for three weeks. Dyspnea had been present on exertion for the past few years. There was no ankle edema, precordial pain, or palpitation. His gastrointestinal history revealed

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anorexia for the past three weeks, associated with constipation. Stools were apparently normal. His genitourinary history revealed nocturia three or four times each night for several years. No dysuria or hematuria.

Examination. On admission temperature was 102.4° F. (rectally); pulse, 100; respirations, 24; and blood pressure, 120/80. The patient was a slender, sallow male, lying comfortably in bed in no distress. There was evidence of considerable loss of weight. Pupils were equal, regular, and reacted to light and accommodation. Nose and ears were negative. The teeth were in poor condition. The tongue was dry and slightly coated. There was no cervical adenopathy or rigidity. There was marked retraction of the supraclavicular fossae. The cardiac impulse was noted lateral to the anterior axillary line. A systolic thrill was felt over the apical area. In this same region a very loud systolic murmur was audible. This was transmitted to the axilla. The same murmur was heard over the entire precordial area and over the base. There was regular rhythm. Breathing at both apices was somewhat bronchovesicular both anteriorly and posteriorly. Numerous moist râles were present at the left base and over the right apex. The liver was slightly enlarged and a tender edge was palpable just below the costal margin. No petechia or icterus was noted. There was moderate clubbing of the fingers. No abdominal tenderness. No edema of the extremities. No impairment of the motor or sensory functions of the extremities. Reflexes were normal. Tentative diagnosis on admission was rheumatic heart disease, pulmonary tuberculosis, or pneumoconiosis.

Admission Laboratory Data.—Red blood count was 3,669,000; hemoglobin, 57 per cent (Dare); white blood count, 14,400, 84 per cent polymorphonuclears, 15 per cent mononuclears, 1 per cent eosinophiles. Blood sugar was 120 mg. per 100 c.c., non-protein-nitrogen, 30 mg. per 100 c.c. The urine was cloudy, amber, acid with specific gravity 1.012, albumin 4 plus. Numerous white blood cells were seen under the microscope. Some of these were in clumps. There were also numerous red blood cells. The sputum was watery. There were a few epithelial cells. No pus cells and no tubercle bacilli were found. (Examination included concentration tests of sputum.) The smears showed chiefly gram-positive cocci, some in clusters, and many fusiform bacilli and spirilla resembling Vincent's organisms.

Clinical Course.—An X-ray film of the chest revealed what was thought to be pulmonary tuberculosis involving the upper halves of both lungs. The heart was situated medially. It gave the impression of being moderately enlarged in all diameters, most markedly to the left. The question of silicosis was seriously debated because of the man's lengthy service as a moulder. The right lung especially showed a generalized fibrosis throughout. On the left side this was present but not so markedly below the fourth rib.

During the first two weeks of the patient's stay in the hospital, chills occurred. These lasted approximately fifteen minutes on each occasion. They were usually three or four days apart and left the patient exhausted. Frequently there was profuse sweating. A productive cough was noted. At times the coughing spells were very severe. On one occasion after coughing there was an expectoration of a large amount of rust-colored sputum and also some sputum streaked with fresh blood. Toward the last two weeks of his illness the patient had occasional epistaxes. Sometimes the bleeding was profuse. The mucous membranes were almost colorless. Transfusion did not seem materially to alter the progress of the disease. Prostration became more and more marked.

After the first week in April the sclerae assumed a subicteric tint. Later the skin color was *café au lait*. Toward the end of the disease, jaundice was marked. Also, after the first week in April a loud diastolic murmur was heard in the pulmonic area. Frequent extrasystoles were observed. The abdomen was spastic and tender throughout. It was slightly tympanitic. Anorexia was severe. The patient was examined

daily for the appearance of petechiae. About the middle of April a single questionable one appeared in each conjunctival sac. A day or two later, examination of the eyegrounds revealed a hemorrhagic area in the left fundus just below and to the right of the optic disc and about three-fourths the diameter of the disc. On that occasion a definite petechia was seen in each of the lower conjunctival sacs, the one on the left having a central pinpoint whitish area. There were also observed several petechiae on the abdomen and in the right axilla. Small ecchymotic areas were present in the right axillary region. A few days later new conjunctival petechiae appeared and then they became very numerous over the chest, abdomen, and back. The spleen was not palpated at any time. During the last ten days it was noted that the left pupil was larger than the right. The tongue protruded slightly to the left and there was moderate nuchal rigidity. The left knee jerk was hyperactive.

With the jaundice, the urine became very dark. Widal tests were negative for typhoid and paratyphoid A and B. No malarial parasites were seen. After the first week in April the blood culture was reported negative. On the tenth of April agglutination test for undulant fever was positive in dilutions of 1:50 and 1:150. No history of drinking goat's milk was obtained. Another blood culture made on April 13 was reported negative on April 16. However, these same flasks on April 23 showed a positive culture of *Brucella melitensis*. The agglutination test remained positive in a dilution of 1:150. Several blood counts during the hospitalization showed only a moderate increase over the original leucocytosis. The differential count remained approximately the same. Repeated examinations of the urine throughout the course showed very much the same picture as at entrance. The sputum remained repeatedly negative for acid-fast bacilli. Wassermann and Kahn tests were negative both on the blood and spinal fluid. The spinal fluid itself was clear. It was under normal pressure. The Pandy reaction was negative. Three mononuclears per cubic millimeter were found in it. A blood culture made on April 18 was reported on April 22 as showing approximately 5,000 colonies of *Brucella melitensis*, per cubic centimeter of blood. The temperature curve was of the septic variety, sometimes swinging up to nearly 105° F. and often subnormal. The pulse varied with the temperature. The respirations were never markedly accelerated.

About the middle of April the patient's blood pressure was only 80/50. With his rapid downhill course he became incontinent of urine and at times delirious. On April 22 his respirations were labored and the pulse was failing rapidly. On that day he died at about 10:50 A.M.

Autopsy.—The post-mortem examination was made by the pathologist, Dr. C. J. Bartlett. The summary of his findings are herewith given: The skin showed a moderate degree of jaundice. There were large numbers of minute petechiae over the front part of the chest and abdomen and also over the back.

On opening the abdominal cavity a small amount of clear liquid was present. The liver extended about one fingerbreadth below the costal margin. There were a few minute petechial hemorrhages in the parietal peritoneum.

There was no liquid in the pleural cavity. There was an old adhesion at each apex. The pericardial sac contained a little more clear liquid than the normal. On opening the heart with aseptic precautions, a vegetation could be seen attached to the mitral valve and a considerable portion of this was removed for culture and microscopic examination. Each side of the heart contained considerable thin liquid blood and soft moist chicken-fat clots. The mitral valve showed a friable vegetation somewhat over 1 cm. in diameter and one other area showed a small granular surface. In the wall of the left auricle there was one small slightly elevated vegetation. The mitral valve showed fibrous thickening in some areas, such as would result from chronic rheumatic valvular endocarditis. The valve was not much shortened and

presumably was competent. The larger vegetation referred to involved both the under and upper surfaces of the valve. This orifice measured 11 cm. The aortic, pulmonic, and tricuspid valves and orifices showed nothing of particular note. The heart weighed 410 grams chiefly due to hypertrophy of the left side. The cavities were somewhat dilated and the myocardium was flabby. The aorta was smooth.

Both lungs showed considerable black pigment. At each apex there was firm scar tissue with a large amount of black pigment. At the left apex this area of scar tissue was greater than at the right and measured about 5 or 6 cm. in diameter. This was the type of scarring which would result from an old tuberculous process though there was an excessive amount of pigmentation. No cavitation was found. Scattered throughout the remains of both lungs were numerous small black areas, some of which were considerably firmer than the surrounding lung tissue. This was interpreted as indicating some degree of silicosis but there was an abundance of functioning lung tissue. Bronchi, a little larger than normal, but no bronchiectatic cavities were recognized. The right lower lobe was congested and there was a little blood on the mucous membrane of the bronchus of this side which presumably came from this lobe.

The spleen weighed 620 grams. It showed numerous recent infarcts varying from 6 or 7 cm. in diameter down to much smaller ones. The pulp was reddish and soft but not so much so as in a typical septic spleen. The Malpighian bodies were readily recognizable.

The pancreas was negative.

The stomach showed several minute petechial hemorrhages in the mucous membrane particularly in the lower half and a very few were found along the course of the intestine.

The liver weighed 1,860 grams. It was in general smooth but on the convex surface of the left lobe, with proper illumination, there could be recognized very minute granules. These were not seen elsewhere. Aside from this the liver and gall bladder were not abnormal.

The suprarenal capsules showed nothing of note.

The kidneys had a combined weight of 415 grams. The capsules stripped readily leaving a smooth surface. The kidneys were pale yellow in color suggesting a mixture of a little bile staining with fatty degeneration. One kidney showed a recent infarct about one and one-half cm. in diameter and the other kidney showed a cyst of about the same size projecting above the cortical surface. A very few minute petechial spots were seen in the kidneys. The cortex was of good thickness. The bladder showed a few petechial spots.

The prostate showed nothing of note. The brain showed a little edema of the meninges. Nothing of note aside from a few minute petechial hemorrhages was recognized.

The anatomical diagnosis was subacute bacterial endocarditis of the mitral valve, chronic mitral endocarditis, myocardial degeneration, scars of old tuberculous lesions at apices of lungs. Some silicosis of lungs, acute infarcts in spleen and one kidney. Fatty degeneration of kidneys, minute petechial hemorrhages in skin and various organs. Slight amount of ascites. Bile staining of tissue in general.

Microscopically the myocardium showed nothing of particular note. The mitral valve showed some chronic thickening together with an acute inflammatory process. The exudate here was chiefly fibrin with comparatively few cells. In a section of the vegetation stained by the Gram-Weigert method there were present in the fibrin great numbers of minute granular structures, probably gram-negative bacilli. A smear made direct from the vegetation before fixation showed many small gram-negative almost coccoid bacilli.

Sections from the apices of the lungs showed dense fibrous tissue with much granular pigment. No tubercles or caseation were recognized. Neither here nor in any of the sections from other parts of the lungs was any active tuberculous process recognized. Sections from some parts of the lungs showed groups of pigment with a little increase in fibrous tissue around this but there was no considerable amount of fibrosis except in the sections from the apices. Sections from the right lower lobe showed a fair amount of blood and some desquamated epithelial cells in the air spaces. The small bronchi also appeared somewhat dilated.

The infarcted portion of the spleen showed the usual picture of acute infarct. Elsewhere there had been a hyperplasia of the spleen pulp with moderate increase in the connective tissue.

The liver and pancreas showed nothing of particular note.

The retroperitoneal lymph nodes showed considerable intercellular hyperplasia.

Microscopic examination of the intestines added nothing to the gross description.

A frozen section of the kidney stained for fat showed a great deal of this in the epithelial cells of the tubules in the cortex. It was in the form of fine droplets and indicated a marked parenchymatous degeneration. Some of the glomeruli showed more partial subdivision than normal and a few of them showed a cellular attachment to Bowman's capsule. Some also showed a few polymorphonuclear leucocytes inside of Bowman's capsule. Hyaline casts were present in some of the tubules. There were some areas of round cell infiltration between the tubules and the cortex. This appeared to be a diffuse inflammatory and degenerative process involving the tubules and to some extent the glomeruli.

The bone marrow of the femur was considerably more cellular than normal.

COMMENT

Since the diagnosis of brucellosis is being made with greater and greater frequency, one should be alert to the possibility of bacterial endocarditis in this disease particularly when the patient has had a history of rheumatic or congenital heart disease. If blood cultures are done by the usual methods, one should not be deceived by the slow growth of the organisms.

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PAROXYSMAL AURICULAR FIBRILLATION IN THE COURSE OF RIGHT HEART FAILURE DUE TO CHRONIC PULMONARY TUBERCULOSIS

CASE REPORT*

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IT HAS been well established that cardiac failure may be produced by a hypertension of the lesser circulation. In this type of failure the increased resistance in the pulmonary circulation results in hypertrophy and dilatation of the right side of the heart. While this condition may be due to a primary obliterating pulmonary arterial disease, it is more commonly due to chronic diseases of the lung.

One of the notable features of this form of cardiac insufficiency is the extreme infrequency of disturbances in cardiac rhythm. This point has been emphasized by White¹ and also by Smith,² who showed that the heart in pulmonary disease characteristically failed with normal rhythm. In a study of right heart failure previously reported³ and in observation of these cases on the Tuberculosis Division for the past five years, this is the first instance of cardiac arrhythmia that we have encountered due only to right ventricular failure.

S. G., a fifty-five-year-old baker, was admitted to the Montefiore Hospital on Sept. 20, 1936, with a history of pulmonary tuberculosis of twenty years' duration. With the exception of a brief period of hospitalization at the onset he had been able to work all the time and complained only of a moderate productive cough. In 1934, following an hemoptysis, there was an exacerbation of the pulmonary tuberculosis, and his condition became progressively worse up to the time of admission. In addition to his pulmonary symptoms he had experienced recurrent attacks of syncope since 1931. These seizures were brief, occasionally associated with convulsions, occurred about twice monthly, and recovery was spontaneous each time.

Physical examination showed the patient to be well developed, well nourished, and comfortable. There were no cardiac symptoms. The heart was not enlarged, there were no murmurs, and the rhythm was regular. The systolic blood pressure was 110 and the diastolic pressure was 60. The liver edge was palpable 2 cm. below the costal border but was not tender. There was no peripheral edema. Roentgen ray examination of the chest disclosed an extensive bilateral tuberculosis of the upper lobes with several large cavities. The cardiac outlines were within normal limits.

The important laboratory data are summarized as follows: Sputum, positive; Wassermann reaction, negative; urine, negative; blood chemistry, negative; red blood cells, 4,290,000; hemoglobin, 82 per cent; white blood cells, 12,500 with normal differential; sedimentation rate, 26 mm. in one hour; venous pressure, 4 cm. of water; electrocardiogram, normal except for low voltage.

*From the Tuberculosis Division of the Montefiore Hospital.

The clinical course in the hospital was characterized chiefly by recurrent large hemoptyses. However there was no remarkable change in his general condition until Nov. 3, 1936, when he suddenly became dyspneic, and examination revealed the pulse to be totally irregular. The cardiac rate at the apex was 140 per minute and the pulse rate was 116. There was no visible venous engorgement or peripheral edema. No electrocardiogram was taken at that time. The patient was rapidly digitalized and completely recovered within twenty-four hours. An electrocardiogram on the following day showed a normal rhythm. On November 14 the patient experienced a similar attack and a tracing taken during the seizure showed auricular fibrillation with a rapid ventricular rate (Fig. 1).

These episodes were repeated at approximately weekly intervals without any manifestations of congestive heart failure until Dec. 7, 1936, when, in the course of another paroxysmal attack, the dyspnea became progressively worse, and the patient became markedly cyanotic. The liver was enlarged to 4 cm. below the costal border, but there was no edema of the extremities. There was no response to therapy, and the patient died on Dec. 9, 1936.

On post-mortem examination the heart weighed 450 gm. There was no pericardial fluid. The right auricle and right ventricle were markedly dilated and hypertrophied, but the left auricle and ventricle were normal in size. The maximum thickness of the right ventricular wall was 10 mm. There was no valvular disease.

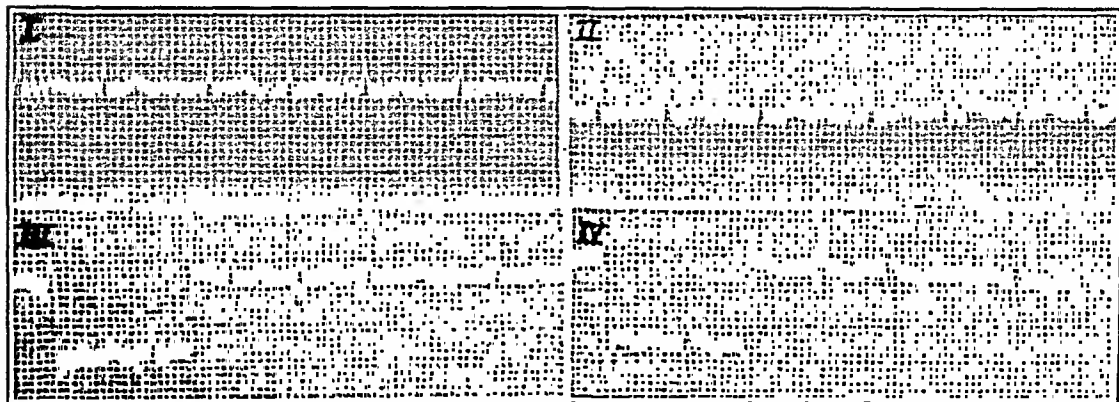


Fig. 1.

The coronary arteries showed slight sclerotic thickening but were patent throughout. Microscopic examination showed hypertrophy of the fibers of the right ventricle. Of interest in the examination of the lungs was the finding of extensive bronchiectasis which was indicative of the long duration of the pulmonary tuberculosis in this patient.

Auricular fibrillation, in itself, has been found on many occasions in patients on the tuberculosis wards. However, it has always been associated with hypertension, coronary artery disease, fibrinous pericarditis, or valvular disease. This is the first instance we have observed in which the only pathological condition found on autopsy was hypertrophy and dilatation of the right side of the heart.

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REVERSIBLE BUNDLE-BRANCH BLOCK IN A CASE OF TOXIC GOITER

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BUNDLE-BRANCH block associated with hyperthyroidism seems to be a rare occurrence. The fortuitous encounter of such a case made follow-up electrocardiographic study necessary in order to determine whether reversion to the normal would occur as is frequently true of inverted T-waves in this disease.

The following case, seen on the cardiological service of Dr. J. B. Wolfe, is presented as an illustration of true reversible bundle-branch block because of a gradual change in the electrocardiographic picture following thyroidectomy rather than an abrupt reversion to a normal rhythm.

Mrs. M. R., aged twenty-nine years, was admitted on July 15, 1936, to the surgical service of Dr. Wayne W. Babcock at Temple University Hospital complaining of palpitation, nervousness, loss of weight, easy fatigability, prominence of the eyes, tremors, intolerance to warm weather but fondness for cold and ability to stand the cold with less covering than is required by the average individual. She stated that she was well until July, 1931, when she began to have the above symptoms. She was put to bed for six weeks by her doctor, who gave her iodine and four or five x-ray treatments to the neck. She felt better for a time, but there was no marked improvement. She became pregnant in 1932 and again in 1934, during which time practically all her symptoms disappeared. Five weeks prior to admission she experienced an exacerbation of the above symptoms and lost 15 pounds. Palpitation became frequent and severe and tremor of the hands so marked that on one occasion she dropped a sugar bowl. She began to have attacks of precordial pain without radiation. She was troubled with constipation, and her last menstrual period (one week prior to admission) lasted only two days whereas it previously lasted five days. There were no other symptoms.

Past medical history included measles, whooping cough, diphtheria, and scarlet fever in childhood. She had had no other illness. She has four children living and well. The family history is irrelevant.

Physical examination showed the following: White young-looking woman, mentally alert, of good color. There was no frank exophthalmos although her expression was somewhat "starey," and the palpebral fissures were somewhat widened. The thyroid was visibly enlarged. The peripheral vessels were soft. The pulse was rapid (120 per minute), equal in both wrists, and synchronous with the heart impulse. The apical impulse was diffused over a wide area and was tumultuous, causing the entire breast to rise and fall with systole and diastole. The cardiac outline was within normal limits to percussion. The heart sounds were loud. There was accentuation of the second pulmonic sound. No adventitious

sounds were heard. There was no evidence of cardiac failure. Laryngoscopic examination was negative. Fine digital tremors were noted. The blood pressure was 150/100. Impression: Toxic goiter.

Laboratory Studies.—Urine was yellow color, acid reaction, specific gravity 1.017, very slight trace albumin, negative sugar, no casts, no red blood cells and no white blood cells.

Blood count showed 70.4 per cent hemoglobin, 4,890,000 red blood cells, color index of 0.73, 5,350 white blood cells, 72 per cent polymorphoneutrophils, 24 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophiles.

Basal metabolism on admission was plus 18 per cent.

Electrocardiographic examinations on July 20, 1936 (Fig. 1), showed left bundle-branch block (new nomenclature) and tachycardia.

Thyroidectomy was performed by Dr. Wayne W. Babcock on July 21.

On July 23 conduction disturbances although still present were greatly diminished.

On Sept. 4, 1936, there was complete absence of bundle-branch disturbance.

Fluoroscopic examination on July 20, 1936, showed that the heart was of normal size, shape, and position. There was no apparent enlargement of any of the

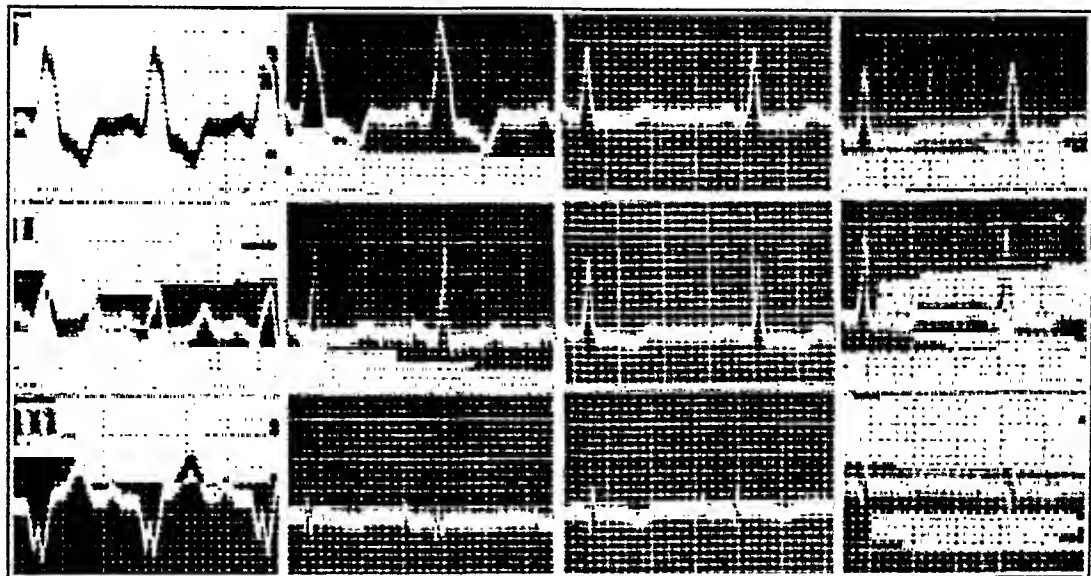


Fig. 1.—Reversible bundle-branch block in a case of toxic goiter.

chambers. The heart was markedly overactive. There was no abnormality of the aorta. The lungs were clear. The diaphragm was quite low.

On July 29 and Sept. 4, 1936, there was no change except that the heart was no longer overactive.

Pathological Report.—Gross description: Specimen consisted of several ragged pieces of pale, beefy thyroid tissue. The largest measured $6 \times 2.5 \times 1.8$ cm.

Histological description: Microscopic sections showed the thyroid to be composed of large areas of more or less solid cellular tissue. Throughout this, tiny acini were seen. Here the picture suggested that of a fetal type of adenoma. In other areas the acini were somewhat larger and partly filled with colloid. The lining epithelium was of the cuboidal type. There were areas of hyalinized fibrosis. The thyroid stroma was cellular throughout with a few collections of small round cells. The diagnosis was involuting toxic goiter.

Sampson¹ quite recently saw a similar patient "who showed a recession from the bundle-branch block form after an acute cardiac episode at the termination of her thyrotoxicosis by thyroidectomy. The changes appeared rather gradually over a period of one week. . ."

DISCUSSION

The cause of bundle-branch block in these cases is uncertain. Sampson feels that "... transient anoxemia of the heart muscle and conduction system" is responsible. Whatever the factor or factors involved, it can be said that bundle-branch block associated with hyperthyroidism may be reversible following appropriate therapy.

The significance of the last statement is apparent when one considers the possibility that a single electrocardiogram showing bundle-branch block may mislead the physician not only in the prognosis, despite a more hopeful outlook, but also in the diagnosis of a given case.

The above cases may be added to those reported by Sampson and Nagle,² Bishop and Bishop,³ Wolff, Parkinson and White,⁴ to modify our ideas regarding the prognostic significance of bundle-branch block.

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4. Wolff, L., Parkinson, J., and White, P. D.: Bundle-Branch Block With Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia. *Am. Heart J.* 5: 685, 1930.

HYPERPYREXIA AS A COMPLICATION OF RHEUMATIC FEVER

REPORT OF A CASE*

JOHN A. BOONE, M.D.
CHARLESTON, S. C.

HYPERPYREXIA occurring during the course of acute rheumatic fever is a dangerous, but fortunately a rather rare complication of the disease. During the past fifty years there has been practically no mention of it in the literature, although the subject is treated at some length in most of the larger systems of medicine. Probably the best discussion, based on 110 cases collected from the older literature and his personal experience, was made by Sir William Church.¹

It would seem to be exclusively an affection of adults, the youngest reported case being seventeen years of age. It is most common between the ages of twenty and thirty years and is rare after fifty. Males are affected more often than females in the ratio of approximately 3 to 2. The majority of instances occur during the first attack of rheumatic fever, the incidence diminishing in repeated attacks, and the mortality is greatest in those cases occurring in the first attack. There is no apparent tendency for an individual patient to have hyperpyrexia again in subsequent bouts of rheumatic fever.

In many the joint symptoms are relatively mild, and the patients are frequently said to have been in a depressed mental state prior to their onset. The appearance of hyperpyrexia usually is preceded by cerebral symptoms, though not uniformly, and most frequently comes in the second week of rheumatic symptoms. The joint manifestations are quickly clouded by excitability that may progress to mania or somnolence and stupor deepening to coma, and convulsions almost invariably supervene. Death from exhaustion or respiratory failure is the rule in untreated cases, and may occur in treated cases. Neither antipyretic drugs nor mild cooling measures have been effective. Only ice baths, promptly given and repeated as often as necessary, seem to have been of any marked value in saving life.

Post-mortem findings as described are very incomplete, since most of the reported cases occurred before histological examination of tissues was generally practiced. Descriptions of gross findings are remarkably negative, little besides congestion of the cerebral vessels and terminal pneumonia being found. The heart valves usually are conspicuously free from anatomical deformity.

*From the Medical and Pathological Services of the Peter Bent Brigham Hospital, Boston, Mass.

Because of the rarity of the condition, the paucity of post-mortem descriptions and the lack of recent literature on the subject, the following case is reported. It is the first case of hyperpyrexia complicating rheumatic fever to be admitted to the Peter Bent Brigham Hospital since it was opened in 1913.

REPORT OF CASE

P. B. B. H. Med. No. 47100.—F. R. K., a forty-year-old native spinster, was admitted to the hospital at 2:30 p.m. on June 25, 1935 in a comatose condition. The family history revealed that the patient's father had died of a "heat stroke," but the history was otherwise irrelevant. As a child she had chicken pox, measles, mumps, and scarlet fever. Ten years before admission she was confined to bed for five months with rheumatic fever, but had no temperature higher than 103° F. at that time. She had frequent mild sore throats, but otherwise had seemed quite well all her life. For the past two years she had been considerably upset emotionally over conditions at her place of employment as a clerk and was given to frequent crying spells at home. Four weeks before entry she developed a nasopharyngitis with some swelling in the neck glands, which persisted several days. Two weeks before entry she noted some stiffness and soreness in various joints, and ten days before entry went to bed with more severe joint pains which were relieved by salicylates administered by her private physician. During the week before entry she began to have periods of irrationality at night, and three days before had a moderate nosebleed. Her temperature tended to rise during the night, but as far as known did not exceed 102° F. The day before admission she began to have a few mild twitching movements of various parts of the body and that night was completely irrational. The morning before admission she seemed stuporous and her temperature was found to be 105° F. She was then sent into the hospital.

Physical examination showed a well-developed and well-nourished middle-aged woman lying limply in bed, comatose, breathing stertorously in infrequent gasps. The rectal temperature was 109° F. (this was the upper limit of the thermometer scale). The pulse was small and thready, the rate 162 per minute. The respirations were not Cheyne-Stokes in character. The blood pressure was not obtainable. The skin was cold and clammy, the face and extremities cyanotic. Scattered over the thorax and abdomen were many tiny serum-filled blebs imparting a rough feel to the skin. Scattered infrequently over the whole body, more especially over the lower legs, were a few petechial hemorrhages. The eyes, including pupillary reflexes and ophthalmoscopic examination, were normal. The breath was foul, the lips and mucous membranes dry and cyanotic. The heart was of normal size, the sounds of poor quality, rapid and regular without murmurs. The lungs showed a few scattered râles and tracheal rhonchi. The abdomen was normal to palpation. No peripheral or tendon reflexes could be obtained.

Laboratory studies showed the blood Wassermann and Hinton reactions to be negative. The urine was clear, with specific gravity 1.011, and showed a very slight trace of albumin. The sediment contained rare red blood cells and a moderate number of coarsely granular casts. The blood showed hemoglobin 70 per cent (Sahli), red cell count 3.8 million, white cell count 27,000 with 75 per cent polymorphonuclears, 13 per cent small lymphocytes, 7 per cent large lymphocytes, and 5 per cent myelocytes. A stained blood smear was otherwise normal. A blood culture was negative. The blood urea nitrogen was 42 mg. per 100 c.c. A lumbar puncture shortly after admission showed normal pressure, Queckenstedt, chemistry, and Wassermann reaction.

Caffeine sodiobenzoate was given subcutaneously and an attempt was made to lower the extremely high temperature by wrapping the patient in a wet sheet and playing an electric fan over it. Under this regime the temperature slowly fell until after two hours it had reached 106° F. At about this time there began small twitchings of the lips and face and gradually the remainder of the body muscles became involved in the twitchings. The temperature continued to fall and by midnight had reached 103° F. The muscular twitching continued to spread and to increase in severity, no effect being had by carbon dioxide inhalations, calcium gluconate intravenously, or sodium phenobarbital subcutaneously. During the last five hours of her life the patient was in a continuous clonic convulsive state. She gradually became exhausted and died fourteen hours after admission to the hospital.

POST-MORTEM FINDINGS

Gross.—The abdominal organs were normal with the exception of two small uterine fibroids and a small ovarian cyst. The heart weighed 280 grams. There were a few petechial hemorrhages scattered over the visceral pericardium but no evidence of pericarditis. In each auricle were small ante-mortem thrombi. The heart valves were entirely normal in appearance. The endocardium showed numerous tiny, slightly raised, white points near the attachments of the tricuspid valves, and three small petechial hemorrhages in the septal portion of the left ventricle. The lungs were normal aside from one small area of atelectasis and a few scattered petechial hemorrhages on the visceral pleura. The brain showed mild diffuse cerebral edema, venous congestion, and a distinct pressure cone at the base, involving cerebellum, pons, and medulla. There was a small meningioma, 4 mm. by 6 mm., over the right frontal lobe. The subarachnoid fluid was clear, showed no organisms or increased cells, and no exudate was seen. Close examination of sections, especially in the region of the basal ganglia, showed nothing abnormal. The superior longitudinal sinus and several of the cerebral veins showed ante-mortem thrombi.

Microscopic.—The heart showed a most striking active rheumatic involvement of myocardium, epicardium, and endocardium, including the mitral and tricuspid valves, as exemplified by Aschoff bodies in large number and in all stages of development. In one of the larger coronary arteries there was a lesion in the intima and media which was interpreted as being of an acute rheumatic type, and numerous vessels contained recent thrombi. One section showed a nerve trunk coursing in the epicardial fat, and involving this nerve was a typical Aschoff body. There was some very slight scarring through the myocardium, interpreted as being probably the healed lesions of the previous attack of rheumatic fever. In the sections from the aortic sinus and the arch of the aorta there was prominent thickening of the adventitia, swelling and fragmentation of the collagen, and numerous strands of fibrinoid material. Into this matrix there was prominent infiltration with monocytes, multinucleated cells, lymphocytes, and small numbers of polymorphonuclear leucocytes. About the numerous small vessels small groups of Aschoff cells were seen. Similar changes were seen in the pulmonary and renal arteries. The remaining viscera showed little of importance aside from frequent fibrinous thrombi in small vessels. Sections of the brain, including cerebral cortex, basal ganglia, pons, medulla, and cerebellum, showed nothing aside from engorgement of vessels with occasional thrombi and slight to moderate edema. Fiber tracts and cells were well preserved. The pituitary showed an area of hemorrhage in the pars intermedia about the size of one low power field. It extended laterally into the interstices of the dense collagen of the dura and slightly into the pars anterior and pars nervosa, but principally it infiltrated the fibrous tissue in the pars intermedia and lay about the euboid-line spaces. It con-

sisted principally of red cells, but there were masses of free pigment and several instances of phagocytosis of pigment. In one region there were a few small strands of fibrin among the cells.

COMMENT

The mechanism of the production of hyperpyrexia in rheumatic fever is quite obscure. The only lesion found in this case that by any chance might be conceived to have been of causative effect was the pituitary hemorrhage, but there is no evidence that such a lesion can cause hyperpyrexia. Granted that such an excessively high temperature is of "cerebral origin," there is a possibility that one of the widespread small-vessel thromboses might have involved the hypothetical "heat center" of the brain.

The case reported was probably beyond any therapeutic measures when first seen in the hospital. It would seem, however, that since hyperpyrexia tends to appear rather late in the rheumatic attack, and nearly always signals its imminence by symptoms of cerebral disturbance, it could be watched for by taking frequent temperature readings and controlled in its early stages by simple physical measures.

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Editorial

THE AMERICAN HEART JOURNAL, under the editorship of Dr. Lewis A. Conner, has attained a position of distinction. Great honor is due Dr. Conner for the service that he has rendered in the development of a journal that is having a significant influence on the progress and practice in this field of medicine. It is hoped that the high scientific and literary standards set by him may be maintained.

The new Editor-in-Chief is aware of his responsibilities, and with the help of the Associate Editors and the Editorial Board, will strive to promote the further development of the AMERICAN HEART JOURNAL.

Fred M. Smith.

Department of Reviews and Abstracts

Selected Abstracts

Hess, W. R.: Central Regulation of Circulation and Respiration. II. International Medical Week, Lucerne, 1936. Abstracted from *Ztschr. f. Kreislaufforsch.* 29: 370, 1937.

The central nervous system coordinates the state of the respiratory and circulatory systems according to the needs of the moment. There is a unity between the nervous system and the physiologic state of the organs affected. The part of the nervous system involved in stimulating respiration and circulation is the sympathetic nerves, and that for conserving their activities is the parasympathetic nerves. The centers are in the medulla and hypothalamus.

L. N. K.

Dressler, Wilhelm: Pulsations of the Wall of the Chest: I. General Consideration. *Arch. Int. Med.* 60: 225, 1937.

Examination by means of simple inspection and palpation is almost always sufficient to demonstrate diagnostically important pulsatory findings. The graphic registration serves merely to control the clinical findings; it should be carried out with the fixed receptor.

Pulsatory movements of the thoracic wall are essentially caused by the effect of change in shape and diminution in volume of the heart. Hypertrophy and dilatation of the right chamber in association with the dilatation of the left auricle, as encountered in cases of lesions of the mitral valve of a severe degree, lead to a forceful systolic propulsion of the precordial area near the sternum.

Systolic depressions of the thoracic wall are due to the centripetally directed movement of the cardiac systole, which exerts an aspiratory effect on the thoracic wall in two ways: (1) directly, when the heart is in contact with the thoracic wall, and (2) indirectly, owing to the fall in intrathoracic pressure caused by systole. The effect of these aspiratory forces on the thoracic wall is equalized under normal conditions mainly by two factors: (1) the oppositely directed propulsive force due to the systolic change in shape of the heart and (2) the expansion of the lungs.

Pathologic depressions of the thoracic wall during systole are due to (1) marked increase of the systolic aspiratory effect (reduction of ventricular volume during the systolic efflux), (2) inhibition of the systolic change in shape of the heart, and (3) inhibition of the expansion of the lungs.

An increase of the stroke volume much more commonly causes systolic depression of the thoracic wall than do adhesions of the pericardium.

The liver may transmit its pulsatory movements to the adjacent thoracic wall. Normally the systolic efflux of venous blood from the liver often causes a depression of the portions of the thoracic wall in front of it. The systolic depression is often particularly marked in the presence of aortic regurgitation; this is due to the

increase in stroke volume and the increased aspiratory effect. Tricuspid regurgitation as a rule causes a forceful systolic propulsion of the hepatic area. The systolic impulse of the blood regurgitating into the large right lobe of the liver transmits to the whole chest a frontal movement directed from left to right. A presystolic propulsion of the thoracic wall over the hepatic area is often noted in congestive failure of the right side of the heart but particularly in the presence of tricuspid stenosis, provided the auricle is still capable of contraction.

In addition to primary pulsatory phenomena, which occur directly at the place of the pulsatory impact, secondary pulsations or associated pulsatory movements are observed. They should be looked on as distinct effects of the primary pulsatory forces. Pulsatory movements of the whole chest in a frontal direction are caused by a compensatory effect of both types of pulsations; this is observed when there is marked hypertrophy of the left ventricle, tricuspid regurgitation, or mitral regurgitation, associated with aneurysmal dilatation of the left auricle to the right.

AUTHOR.

Hallock, Phillip, and Benson, Ikel C.: *Studies on the Elastic Properties of Human Isolated Aorta.* J. Clin. Investigation 16: 595, 1937.

A method for experimentally obtaining the volume-elasticity coefficients of isolated aortas has been described.

The mean volume-elasticity curves demonstrate that arterial rigidity increases, (a) progressively with age and (b) with increasing diastolic pressure.

The aorta of old age assumes the rôle of a capacity chamber or reservoir and by virtue of this readjustment it becomes adapted to the reception of the cardiac output without imposing an undue strain on the heart, a condition which would otherwise result if the disappearance of elastic tissue occurred without a concomitant increase in the diameter and length of the aorta.

If the pulse wave velocities are calculated from mean volume-elasticity curves and compared with the mean pulse wave velocities obtained in living man at corresponding ages, it is found that the mean values obtained on the isolated aorta are less than those obtained in vivo by about 6 per cent. In the study of isolated aortas, the velocity values are slightly low due largely to the factor of elastic "after-action."

Due to the satisfactory agreement of the pulse wave velocities found in vivo and in the isolated aortas it is possible to evaluate the condition of the aorta in living man by comparison with an isolated aorta having approximately the same pulse wave velocity.

AUTHOR.

Levine, Samuel A.: *Presence of Digitalis in Body Fluids of Digitalized Patients.* Arch. Int. Med. 60: 240, 1937.

A patient with cardiac disease who is digitalized and who yet shows peripheral edema or free fluid in the body cavities occasionally has symptoms of headache, nausea, vomiting, giddiness, and lassitude after diuresis induced with salyrgan or mercurin or with theophylline. These symptoms could be due to digitalis intoxication when the body fluids are excreted through the kidneys by way of the blood stream, if that body fluid contained digitalis substances.

On the basis of the chemical method of Schmidt, modified in terms of the physical properties of digitoxin, edema fluid from the pleurae, peritoneum, and leg was treated and concentrated, with the recovery of a gray white precipitate. This

precipitate, suspended in Clark's solution, was placed in a Straub preparation of the frog heart to be tested for digitalis, and the results were recorded on a kymogram. These curves were compared with curves for known digitalis.

A total of twenty-nine specimens of fluid from twenty-four patients was examined. Eighteen fluids were from known digitalized patients. Thirteen of these gave positive evidence of digitalis by the biologic method. The results were questionable in four cases and negative in one case. Two specimens from patients with questionable digitalization gave doubtful results. Nine specimens of fluids from patients with tuberculosis, neoplasm, or cirrhosis of the liver, none of whom had been given digitalis, were used as controls. None of these showed any digitalis effect.

Although no exact quantitative determinations were carried out for the thirteen fluids showing curves indicative of a digitalis effect, we believe the amount recovered was significant and sufficient to cause clinical symptoms in patients under the conditions discussed.

The Knudson-Dresbach reaction for the quantitative determination of digitalis glucosides was unsatisfactory in our experience. The qualitative Keller-Kiliani test for desoxycarbohydrate, though not specific and not highly sensitive, gave positive reactions for five of eleven specimens of fluid showing the digitalis effect by the biologic method.

It is believed that active digitalis substances are present in the body fluids of digitalized patients and that they can be recovered. Further studies are necessary, however, to confirm or to discredit the idea that these substances may give rise to symptoms of digitalis intoxication following diuresis.

AUTHOR.

Condorelli, L.: The Pneumomediastinum in Cardiological Diagnosis. *Cardiologia* 1: 26, 1937.

The author describes his anatomical investigations and presents evidence in favor of a "septum fibrosum" between the anterior and posterior pneumomediastinum. The significance of pneumomediastinum in cardiological diagnosis is discussed, with special reference to the condition of adherent pericarditis.

AUTHOR.

Mahaim, I., and Benatt, A.: Studies on the Superior Connections of the Left Branch of the Bundle of His-Tawara With the Interventricular Septum. *Cardiologia* 1: 61, 1937.

In men there are branches from the left bundle of His which supply the muscle of the interventricular septum. These arise high up near the bifurcation of the main bundle.

These branches are very small and can only be demonstrated by most careful and systematic investigation. In normal conditions they are of very little importance but they may account for some anomalous results observed in clinical cases of branch-bundle lesion.

AUTHOR.

Blumberger, K.: The Differentiation of Two Types of Sino-Auricular Block. *Deutsche med. Wchnschr.* 62: 1377, 1936.

Partial S-A block can be differentiated in much the same way as A-V block. The one type shows the equivalent of the Wenckebach period; the second does not.

L. N. K.

Geraudel, E.: A Case of Auriculo-Ventricular Dissociation With Tachycardia. *Cardiologia* 1: 9, 1937.

The author describes a case of sinus tachycardia with partial block which he has observed for fourteen years. The frequency varied from 120 to 200 per minute. Occasionally, the records showed signs of heart block. The relations of the observed changes to auricular flutter are discussed.

AUTHOR.

Kisch, Bruno: Intermediate Waves in the Electrocardiogram. *Cardiologia* 1: 17, 1937.

Attention is drawn to the occasional occurrence of certain typical positive waves in the electrocardiogram which have not been previously considered. These are the following:

There are two extra waves between R and Q, one immediately following P and the other immediately preceding Q. If Q is absent the latter precedes R. There is another wave between S and T, or if S is absent between R and T.

AUTHOR.

Sigler, Louis H., Stein, Isidore, and Nash, Philip I.: Electrocardiographic Changes Occurring at Death. *Am. J. M. Sc.* 194: 356, 1937.

Electrocardiographic studies were made on 20 cases before, during, and after clinical death. The changes noted were: sinus tachycardia, followed by sinus bradycardia and sinoauricular standstill; development of ectopic foci of irritability, resulting in nodal rhythm, single and multifocal ventricular premature contractions and ventricular paroxysmal tachycardia; appearance and disappearance of auricular activity; auriculoventricular block in various degrees; ventricular fibrillation; marked changes in the initial and terminal ventricular complexes; intraventricular conduction disturbances in various degrees up to bundle-branch block. In many cases the electrocardiographic manifestations were noted as long as one hour after clinical death.

The factors responsible for these electrocardiographic changes appear to be disturbances in the vagosympathetic control of the heart, anoxemia, toxemia, and local nutritional and ionic disturbances in the heart. That anatomic disease of the heart itself is not responsible for the ultimate manifestations is evidenced from the fact that these changes occurred in the normal as well as in the diseased hearts. The sinus slowing and standstill, as well as the various grades of auriculoventricular block, appear to be mainly of vagal origin. Intraventricular disturbances are dependent on the other factors. The latter disturbances depict changes in the distribution of the excitation waves and the order of excitation and retraction as well as transient focal blocking and localized partial or total refractoriness.

AUTHOR.

Weiss, Soma, and Wilkins, Robert W.: Myocardial Abscess With Perforation of the Heart. *Am. J. M. Sc.* 194: 199, 1937.

The two cases of solitary myocardial abscess with perforation of the heart are described. In the first case the abscess, caused by *S. aureus*, ruptured into the right ventricle as well as into the pericardial sac. In the second case the abscess, caused by pneumococcus, was localized mainly in the fat tissue at the junction of the auricle and ventricle and was formed as a direct extension of a small mural pneumococcus

vegetation. This abscess ruptured into the pericardial sac. In both cases the clinical course did not suggest sepsis and the unexpected cardiac perforation resulted in a fatal circulatory collapse.

While abscess of the myocardium in cases of sepsis is not an unusual occurrence, perforation of the heart by abscess is rare. Seven such instances, collected from the literature, are cited. As judged from the nine cases now available, myocardial abscesses are silent until their rupture causes sudden low thoracic pain, followed by circulatory collapse. In two of the nine cases a diastolic murmur was present.

AUTHOR.

Narat, J. K.: A New Electrical Stethoscope. *Ztschr. f. Kreislaufforsch.* 29: 313, 1937.

A contact Rochelle crystal microphone was used with a button attached to be placed against the chest. The current is amplified by a 4-stage radio amplifier and through a tone filter. This method is also used for pulse records. Records were made on film.

L. N. K.

Molz, B.: A Method of Obtaining Unipolar Leads in the Electrocardiogram. *Ztschr. f. Kreislaufforsch.* 29: 361, 1937.

Previous methods of obtaining unipolar electrocardiograms are not free of theoretical objections. A new method is described. A person is placed up to his neck in a wooden bath containing warm conducting solution and an extensive wire mesh. The wire mesh gives the potential of the entire body and this shows practically no change during the heart beat. This mesh is used as the indifferent electrode.

L. N. K.

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No. 2

Original Communications

APNEA OR CONVULSIONS FOLLOWING STANDSTILL OF THE HEART*

CLINICAL AND EXPERIMENTAL OBSERVATIONS

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AMSTERDAM, HOLLAND

ONE of the most dramatic diseases known is the syndrome of Adams-Stokes caused by periodic standstill of the heart. The effect of sudden interruption of the supply of blood to all organs, more especially of that to the brain, is violent. About ten seconds after disappearance of the pulse, sudden loss of consciousness usually occurs, and later severe convulsions may appear. It may be assumed that convulsions are, under these circumstances due to anoxemia of the brain, for Kussmaul and Tanner showed in 1853 that convulsions, similar in nature to these, may be readily produced by clamping off its four main arteries. The sensitivity of the respiratory center to anoxemia is now well known and cessation of function of this center *during* long attacks of Adams-Stokes syndrome may not only be expected to occur theoretically but can sometimes actually be observed.

The present study is concerned with physiological disturbances, cerebral in origin, which occur not *during* the attack of cardiac standstill but almost immediately *after*. These cerebral symptoms consist of (a) cessation of respiration (period of apnea) and (b) convulsions. Doubtless similar phenomena have been observed by many authors, but they have been universally described as Cheyne-Stokes breathing. Most authors believe that Adams-Stokes attacks give rise to Cheyne-Stokes breathing through anoxemia of the brain. The most accurate account of this sort of apnea has been given by Griffith.⁴ He describes a case in which the period of apnea had a constant and peculiar relationship to the period of standstill of the heart. It did not begin until after the

*A preliminary report of this subject was read in the Deutschen Gesellschaft für Kreislaufforschung, 8. Tagung. 1935.

From the Medical Service of the University of Amsterdam, Director, Professor Dr. I. Snapper.

period of asystole had passed off; there was occasionally even an interval of a few seconds between the end of asystole and the beginning of apnea. They never coincided in time. In other attacks, clonic muscular spasms of moderate violence came on a few seconds after return of the pulse. Similar phenomena have been described by Averbuck,¹ Dlugacz,² Grassberger,³ and others.

Wenckebach and Winterberg⁵ described a somewhat different sort of case in which a period of apnea *preceded* the period of asystole. They assumed therefore that apnea was the cause of asystole. They were able to show after Cheyne-Stokes breathing had almost disappeared that a voluntary pause of breathing induced a period of asystole, just as the spontaneous periods of apnea had done earlier in the illness. They explained the phenomenon by assuming that the action of anoxemia upon the automatic ventricular center leads to inhibition. A case similar to theirs in some respects will be described later in this article (Case 3). Since the descriptions of the attacks of asystole with apnea and convulsions and the theories as to their relationship did not seem satisfactory to us, we deemed it advisable to study the phenomena more carefully in an attempt to explain them on the basis of well-known and established physiological facts.

Views of the physiology of respiration, and of the relation between respiration and circulation have become clearer in the past few years. It has been shown that pulmonary ventilation is mainly regulated by the carbon dioxide content of the arterial blood. Increase in concentration of carbon dioxide in the blood results in increase in acidity to which the respiratory center responds by increasing the ventilation. In this way more carbon dioxide is given off through the lungs, and the normal arterial content of carbon dioxide and normal acidity of the arterial blood is reestablished. Conversely, decrease in the content of carbon dioxide in the arterial blood results in a shift in its reaction toward the alkaline side, decrease or even cessation of ventilation, retention of carbon dioxide and again reestablishment of the normal level of acidity of the blood. The respiratory center is, because of this mechanism, one of the most important factors in maintaining constant the degree of acidity of arterial blood. Heymans has found that chemical and physical stimulation of the carotid sinus may in addition have a profound influence upon the respiratory center.

A constant concentration of carbon dioxide in the arterial blood can be assured only by very accurate reciprocal adjustment between respiration and circulation. Disturbances of the carbon dioxide level in arterial blood are mainly due to three factors; changes in rate of (1) ventilation, (2) circulation, and (3) production of carbon dioxide. Either hyperventilation or decrease in volume of circulation alone, without change in the other two factors, will be followed by a lowering

of arterial carbon dioxide, and consequently a decrease in ventilation. It becomes clear then how a period of complete cessation of the circulation affects profoundly chemical equilibrium. A study of the nature of the disturbance seems to have been neglected by physiological and clinical investigators—at least I have not been able to find a single paper on this subject in the literature. My interest in the problem was aroused by clinical observation of five patients with complete heart block and attacks of Adams-Stokes disease. These observations suggested that disturbances of respiration or convulsions following temporary arrest of the circulation are due to the sudden arrival at the periphery of hyperventilated blood from the lungs ejected by the first few cardiac contractions following a period of asystole.

CLINICAL OBSERVATIONS

CASE 1.—A man eighty-three years of age was suffering from complete heart-block and frequent attacks of cardiac asystole. The sequence of events observed was as follows: First the pulse disappeared; some seconds later the patient said that an attack was coming on. Shortly afterward he became suddenly unconscious and

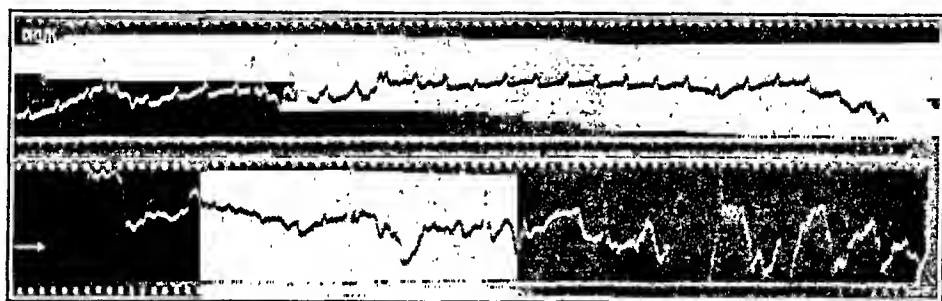


Fig. 1.—Case 1. Attack of standstill of the heart. The lower record is continuous with the upper. In the beginning total A-V dissociation is seen. After two contractions the ventricles cease beating, while the auricles continue. At the end of the upper record the string moves out of the field because of movement on the part of the patient (not a convulsion). The string reappears in the lower record, and shortly afterwards ventricular contractions start again. After the third, severe tonic and clonic convulsions cause continuous movement of the string.

turned very pale; respiration continued, and became deep and frequent. During the attack there were some movements, but no convulsions. Return of the pulse signalized the end of the attack. Some seconds later his face became very red. At the same time severe clonic contractions began, and lasted for about ten seconds (Fig. 1). This peculiar sequence of events was present in every attack that was observed.

CASE 2.—A man fifty-eight years of age with frequent attacks of Adams-Stokes syndrome was under observation during the four days preceding his death. At first, the same phenomena as in Case 1 were observed. After each attack of asystole, convulsions together with an intense flush of his face appeared after an interval of exactly six seconds. The fourth day, after an attack of cardiac standstill of unusually long duration (several minutes) a remarkable change was seen. Unconsciousness, not convulsions, followed the attack and persisted until death. In this state many shorter periods of asystole occurred which, instead of being followed by convulsions, were followed at exactly the same interval (six seconds after cessation) by the period of apnea beginning simultaneously with flushing of the face, and lasting ten seconds.

CASE 3.—A woman seventy-six years of age with complete heart-block and occasional Adams-Stokes attacks was given barium chloride. During the use of this

medication many severe attacks occurred. When administration of the drug was stopped, the frequency of the attacks fell off to the former rate. After each attack a period of apnea was observed to occur coincident with flushing of the face. In this patient we were able to study the phenomenon by simultaneous records of respiration and of the electrocardiogram (Fig. 2).

CASE 4.—A man thirty-seven years of age in good health, except for painful mastitis, developed during examination sudden syncope with loss of consciousness,

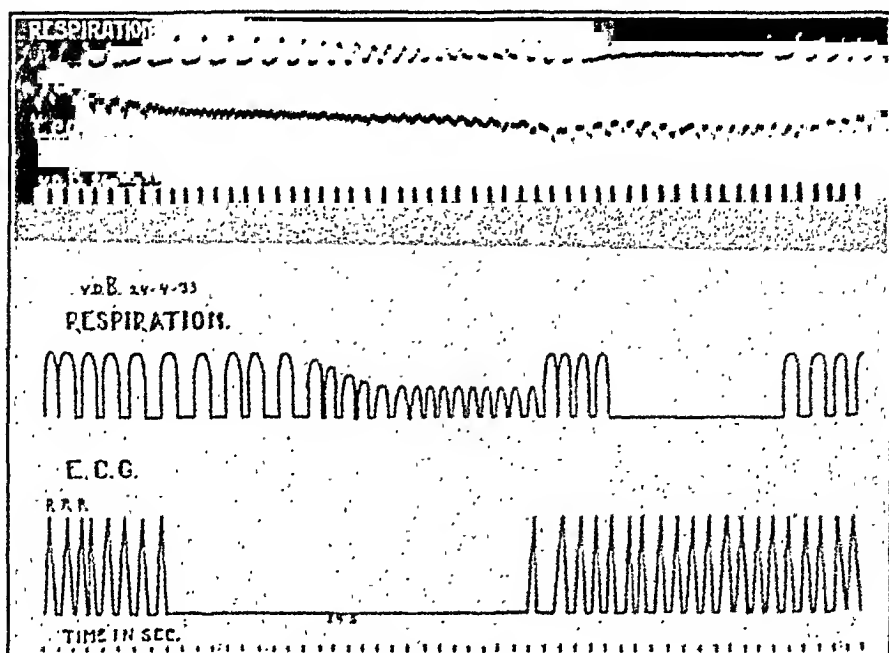


Fig. 2.—Case 3. An attack of standstill of the heart lasting twenty-four seconds is represented. Above, the original simultaneous record of respiration and electrocardiogram in a slow-moving film is shown. Below, the record is schematically drawn (auricular contractions are omitted). Note continuation of fast, shallow respiration during standstill of the heart. After return of ventricular contractions an immediate change of type of respiration (slower and deeper) occurs, probably reflex in origin. Some seconds later a period of apnea begins.

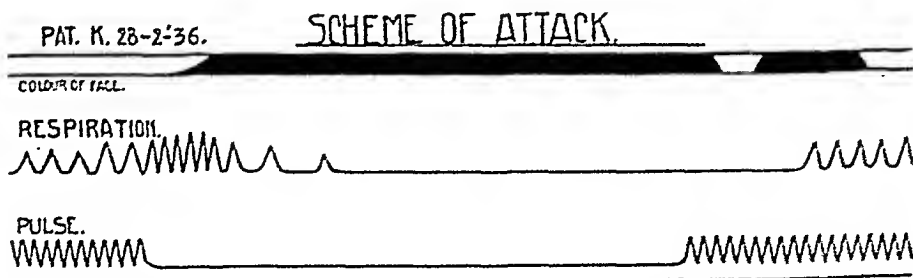


Fig. 3.—Case 5. Reconstruction of the sequence of events during and after an attack of Adams-Stokes syndrome, on the basis of observation. In the scheme for the color of the face, black indicates cyanosis, white the normal red color.

waxen pallor of the face, and disappearance of the radial pulse. After a short time there was a sudden flush of the face, and at the same time some symmetrical clonic contractions of the arms. The phenomena were identical with those observed in the first patient (Case 1). The reaction was somewhat less violent. Since this time, similar observations have been repeatedly made by different colleagues in instances of syncope following venepuncture.

CASE 5.—A woman forty years of age entered the neurological clinic because of frequent attacks of unconsciousness associated with convulsions. During the preceding six years these had been considered to be true epilepsy. Clinical observation showed that this diagnosis was not the proper one and that the attacks were due to Adams-Stokes attacks. By courtesy of Professor Bronwer and Dr. Drooglever Fortuyn I had the opportunity of observing an attack. It began with some acceleration of respiration, and disappearance of the radial pulse. Respiration continued for some time, then became slow, shallow, and stopped altogether. At this point both circulation and respiration had ceased. The face became gradually very cyanotic. Artificial respiration by compression of the thorax was tried without success. Then suddenly the radial pulse reappeared but apnea continued. A few seconds later there was a sudden red flush of the face followed rapidly by a return of marked cyanosis. Finally, respiration began and gradually the normal color of the face returned (Fig.

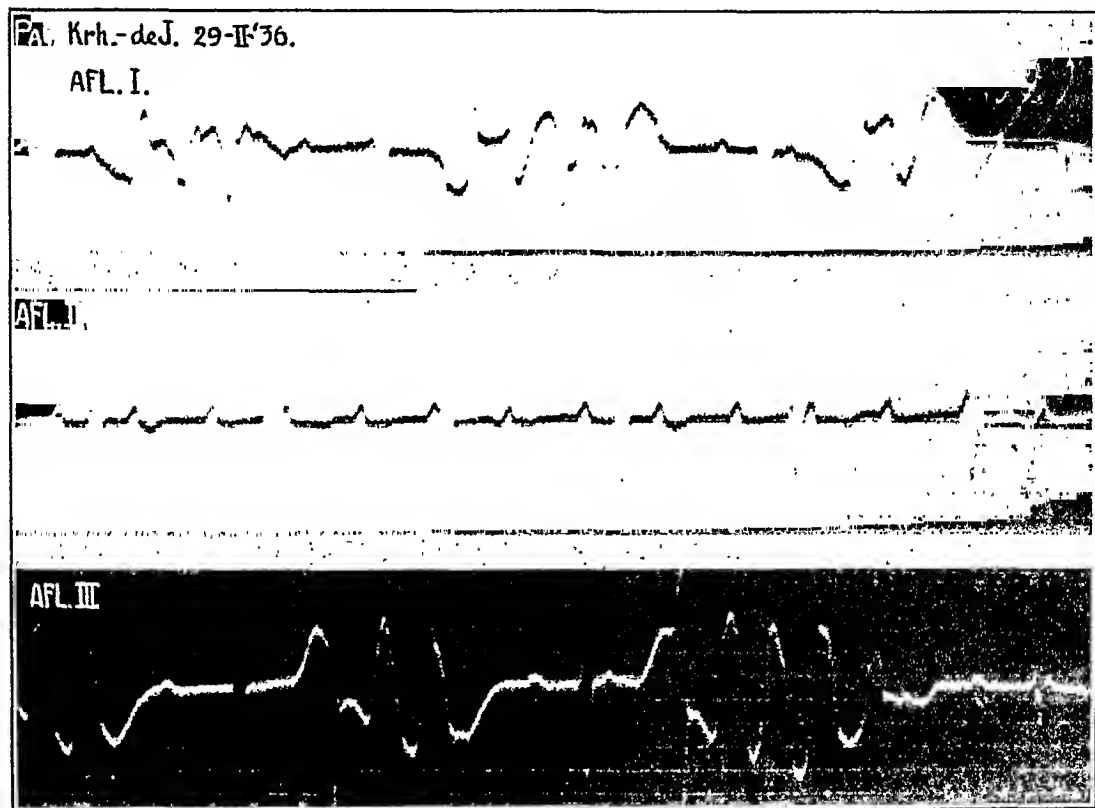


Fig. 4.—Case 5. Electrocardiogram made on Feb. 29, 1936. Total A-V dissociation. Series of ventricular premature beats.

3). An interpretation of this series of events is as follows: First, cessation of circulation with increased ventilation led to hyperventilation of the blood. Second, circulation and respiration both ceased. The hyperventilated blood stayed in the lungs without marked change. There was only a small gain in carbon dioxide and loss in oxygen from the metabolism of lung tissue. Third, reestablishment of circulation occurred with consequent transportation of the hyperventilated blood from the lungs throughout the body as indicated by the transient flush of the face. The respiratory center could not react as it had not yet recovered from prolonged anoxemia. Fourth, the hyperventilated blood from the lungs was followed by blood from the tissues laden with carbon dioxide and poor in oxygen; the latter passed the lungs unchanged as respiration was still absent. Fifth, recovery of respiration was stimulated by circulation of blood with increased content of carbon dioxide from the tissues. The patient was given ephedrine without effect and the next day was transferred to the medical service. An electrocardiogram (Fig. 4) was then obtained.

Complete heart-block was present and frequent ventricular premature beats occurred, sometimes in series of three or four. A tentative diagnosis of Adams-Stokes attacks due to ventricular fibrillation was made. It was confirmed later by a record obtained

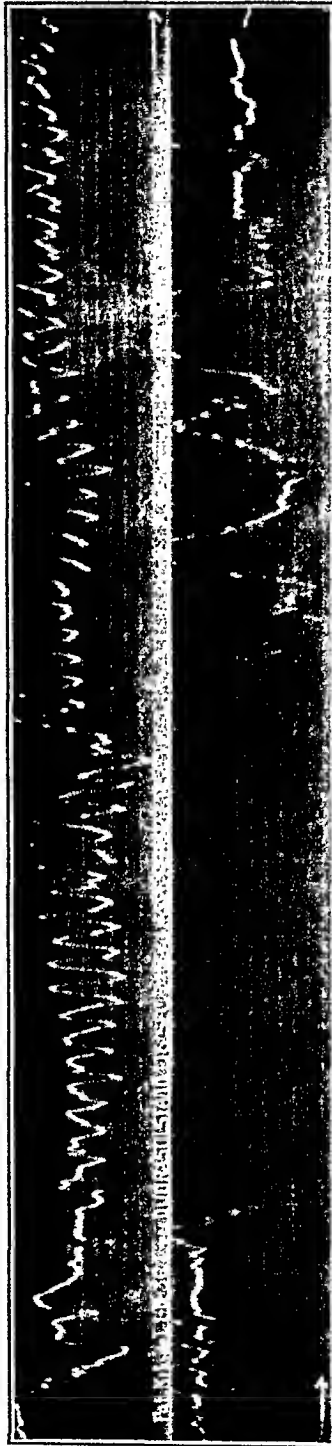


Fig. 5.—Case 5. Attack of ventricular flutter lasting sixteen seconds. Immediately after the first isoelectric stretch (reestablishment of coordinated ventricular contractions) the occurrence of severe clonic convulsions is indicated by the violent movements of the string.

during an attack (second observed attack) accompanied by absence of the peripheral pulse (Fig. 5). The electrocardiogram showed a succession of very rapid electrical waves. It is doubtful whether these should be regarded as ventricular flutter or as fibrillation. The effect on the circulation was, as far as could be judged from clinical observation, the same as that of ventricular asystole. During the attack there was

continuation of respiration and absence of convulsions. Very soon after the end of the attack, marked in the electrocardiogram by the first isoelectric stretch, severe convulsions occurred.

That a period of apnea invariably followed an attack of cardiac standstill strongly suggested that the sequence was not fortuitous but the logical and necessary outcome of existing relations between circulation and respiration. During cardiac standstill the circulation must practically have ceased. The stagnant blood in the lungs was however continuously ventilated because respiration was uninterrupted. This blood therefore undoubtedly gained oxygen, probably to complete saturation, and lost large amounts of carbon dioxide. At the end of

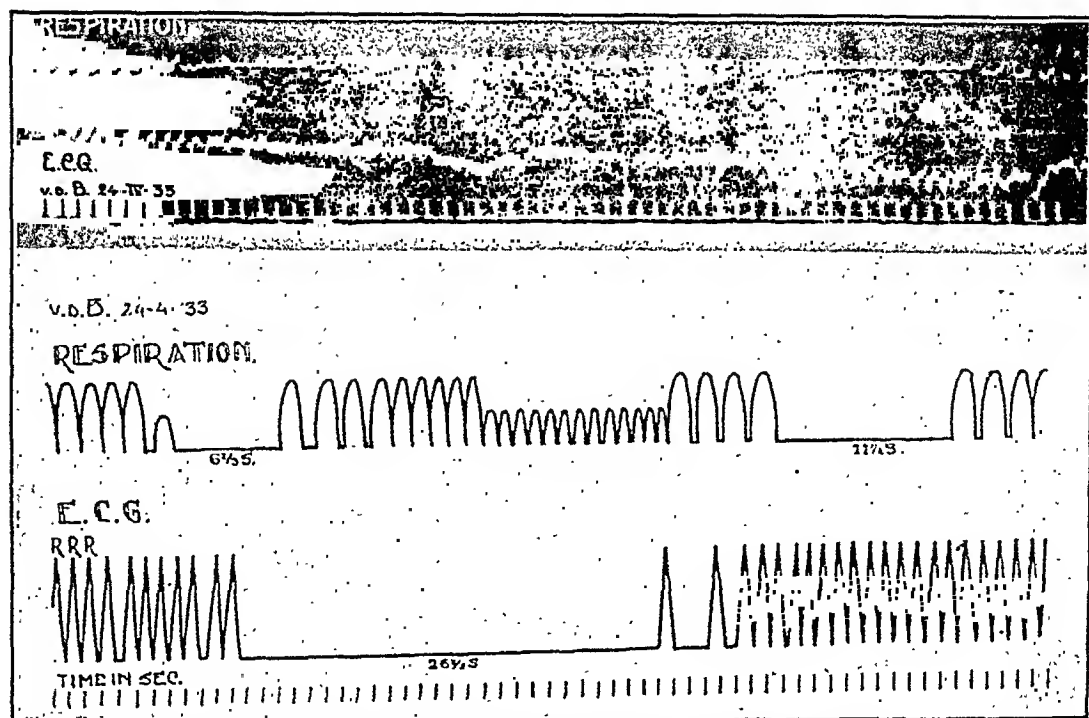


Fig. 6.—Case 3. An attack of standstill of the heart lasting twenty-six seconds is shown. It is preceded and followed by a period of apnea. Above, is the original record; below, a schematic drawing.

the period of cessation of circulation the lungs were apparently filled with intensely hyperventilated blood, rich in oxygen but very poor in carbon dioxide. The first few cardiac contractions would then suddenly distribute this blood throughout the body and what is more important, to the respiratory center as well. The reaction of the center would, of course, be to call forth a period of apnea until blood from the tissues, rich in carbon dioxide, arrived. We have seen that in the first patient, and also temporarily in the second, not apnea but convulsions were observed at this time. It seems probable that convulsions can also result from the reaction of the cerebrum to this abnormally hyperventilated blood.

The objection that the phenomena described were merely reactions of a disease or abnormal cerebrum may be raised. The first three

patients were obviously of advanced age and suffering, probably, from arteriosclerotic disease of the heart. Their brains may, therefore, not have been normal. This fact may be of some importance in Case 3, but it is plain that at least convulsions and flushing of the face, the two most frequently associated phenomena, may be seen in quite normal, perhaps only vasolabile, individuals (Case 4).

In addition to a period of apnea following each attack of asystole, one was inconstantly observed in Case 3 preceding the period of cardiac standstill (Fig. 6). It is evident that the same explanation will not suit both situations.

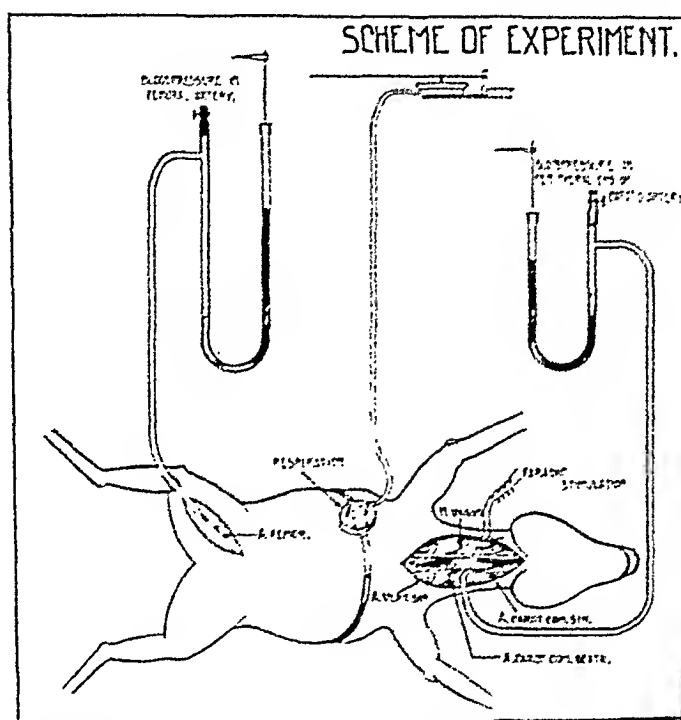


Fig. 7.—A rough sketch is shown of the arrangement of the manometers, the respiratory recorder, and stimulator for the experiments upon dogs and cats.

Another fact seems clear. The occurrence of convulsions or apnea and flushing of the face after cessation of the circulation is obviously not dependent on the cause of the cessation since they follow both cardiac asystole and ventricular fibrillation or flutter. One other point deserves comment. In Case 5 convulsions occurred not after the first very long attack but after the second shorter one. A possible explanation is that in the first observed attack (Fig. 3) hyperventilation was followed by apnea while the circulation was nonexistent; during this time (cessation of both circulation and respiration) hyperventilated blood may have remained in the lungs long enough for the metabolic processes there to produce enough carbon dioxide and probably lactic acid partially to counteract, by diminishing the alkalinity of the blood, the effect of the preceding hyperventilation.

So far argument has been built exclusively upon clinical observation and deduction. More convincing evidence for the theory that the observed phenomena are due to sudden distribution of the hyperventilated stagnant blood in the lungs is difficult to obtain from the study of patients because individuals with this disorder are rare, and also

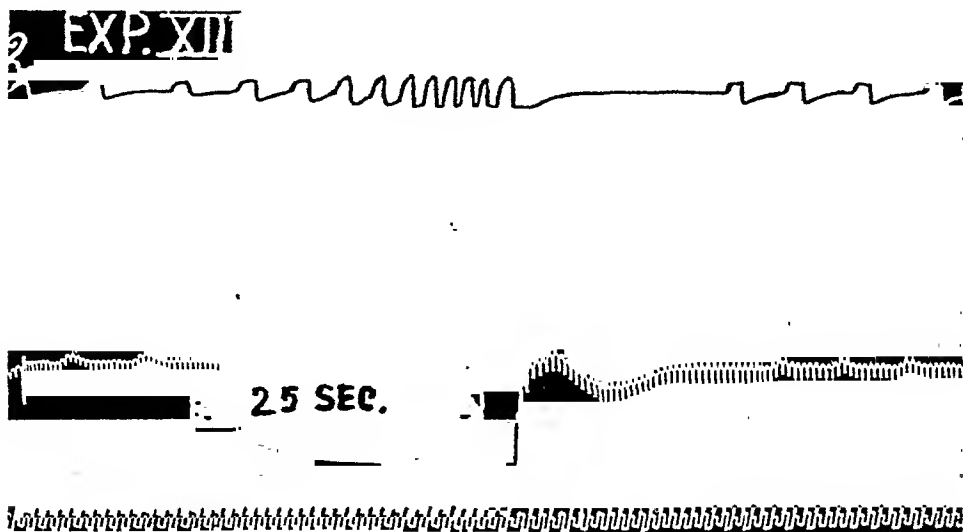


Fig. 8.—Experiment XIII. Dog in morphia-pernocton narcosis. Upper curve—respiration. Lower curve—tension in femoral artery. A record of standstill of the heart for twenty-five seconds is shown. After contractions of the heart return, a period of apnea occurs. In this figure and in Figs. 9-15, inclusive, cardiac standstill was induced by faradic stimulation of the peripheral end of the right vagus nerve.

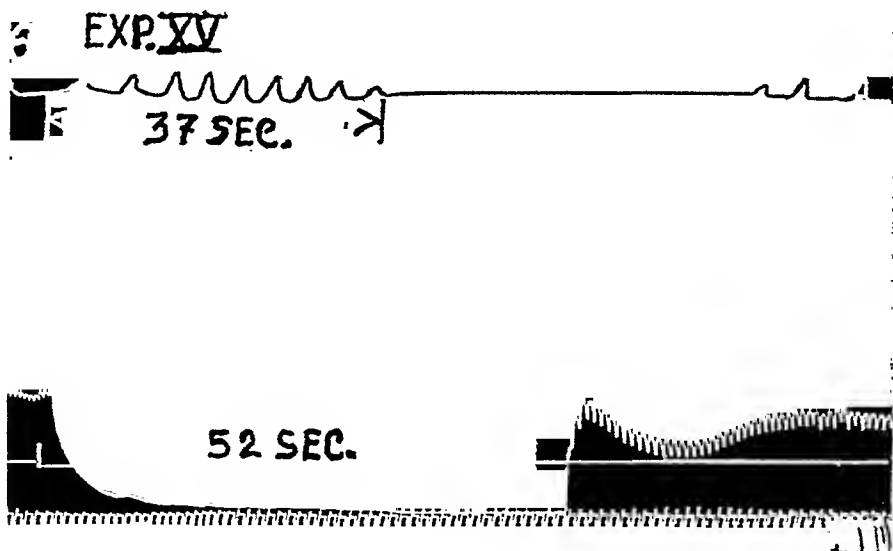


Fig. 9.—Experiment XV. Dog in morphia-pernocton narcosis. A record of standstill of the heart for fifty-two seconds is shown. Apnea begins during cardiac standstill.

because other mechanisms, for example, reflexes from the carotid sinus, may under these circumstances play a part. An attempt was therefore made to reproduce the phenomena in animals.

In dogs, temporary cardiac asystole can often be obtained after isolation and section of the right vagus nerve, through faradic stimulation

of the peripheral end (Fig. 7). Asystole of less than about ten or fifteen seconds' duration was not followed by disturbances of the respiration but when it lasted from fifteen to thirty-five seconds a well-marked period of apnea regularly followed it just as in Adams-Stokes attacks in patients (Fig. 8). When periods of asystole exceeded thirty-five to forty seconds, apnea started *during* them, and lasted some time after recovery of the circulation (Fig. 9). This type of apnea, namely, that which began *during* standstill of circulation, was

EXP. XXI

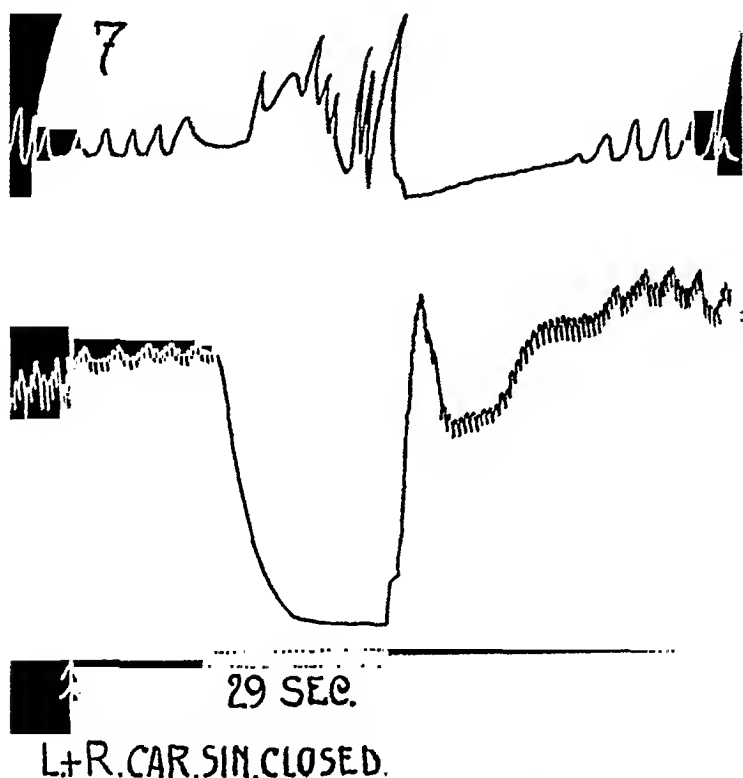


Fig. 10.—Experiment XXI. Dog in morphia-pernocton narcosis. Occlusion of all blood vessels leading to and from both carotid sinuses was completed at arrow. Standstill of the heart for twenty-nine seconds is still followed by a period of apnea.

attributed to prolonged anoxemia of the respiratory center. It was observed also on one occasion in a patient (Case 5). The apnea occurring after asystole of moderate duration (fifteen to thirty seconds) was subjected to further analysis.

Experiment I.* When both carotid sinuses were excluded from the circulation by clamping off all the branches to and from it, the period of apnea appeared in the same manner as before clamping (Fig. 10). This experiment was repeated in

*This numeration of experiments is made for convenience and does not correspond with the numbers of the actual experiments mentioned in the figures.

different dogs and seems to justify the conclusion that the period of apnea is not dependent upon carotid sinus reflexes.

Experiment II. When the carotid and vertebral arteries on both sides were isolated and clamped, almost no effect was observed on respiration in the narcotized animals. Life was possible for a very long time and Kussmaul-Tanner convulsions were not seen. The collateral circulation furnished apparently adequate nourishment for the brain so that loss of cerebral reflexes did not occur. Heymans has shown that some cerebral centers, including the respiratory center, can endure prolonged anoxemia and recover. A very small circulation can maintain the respiratory mechanism intact.

The effect of the collateral circulation on the maintenance of arterial pressure to the brain was measured by recording the pressure in the *peripheral* end of a carotid artery, before and after clamping the three other principal arteries leading to the

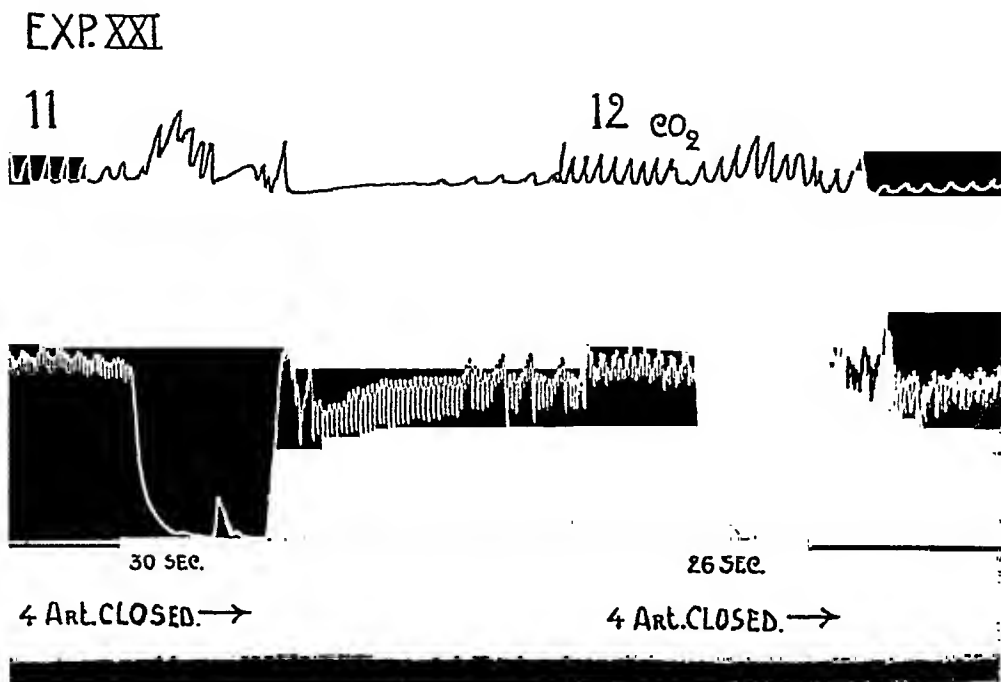


Fig. 11.—Experiment XXI. Dog in morphia-pernocton narcosis. Both carotid and vertebral arteries were clamped before the experiment. During inhalation of oxygen, asystole for thirty seconds (interrupted by one ventricular contraction) is followed by apnea (11). During inhalation of a mixture of oxygen and 5 per cent carbon dioxide asystole for 26 seconds is not followed by apnea (12).

brain. In dogs the pressure here is only about 20 mm. Hg before clamping the arteries and is extremely low afterwards. Now when cardiac contraction was inhibited by faradic stimulation while the four arteries to the brain were clamped, apnea still occurred after the period of standstill (Fig. 11). Apnea was therefore not the result of a sudden rise of blood pressure in the brain or in the carotid sinus since the rise was, in this experiment, insignificant.

Experiment III. The effect of inhalation of a mixture of 5 per cent carbon dioxide and oxygen on the appearance of apnea after vagal inhibition of the heart was studied, because this concentration of carbon dioxide prevents loss of the gas from the blood resting in the lungs. Its use regularly prevented the occurrence of apnea while inhalation of oxygen alone failed to do so (Figs. 11, 12, and 13).

Experiment IV. Direct proof of the passage of hyperventilated blood through the body was obtained by taking samples of blood from the carotid artery immediately after the period of asystole. The color of this blood was redder than

normal arterial blood; the carbon dioxide content was much decreased. For example hyperventilation was sufficient to reduce the carbon dioxide content of the arterial blood more than 4 volumes per cent (from 49.04, 49.09 to 44.88, 44.83 volumes per cent).

In a few experiments mild clonic contractions were observed during the period of apnea, analogous to the convulsions observed in patients with Adams-Stokes

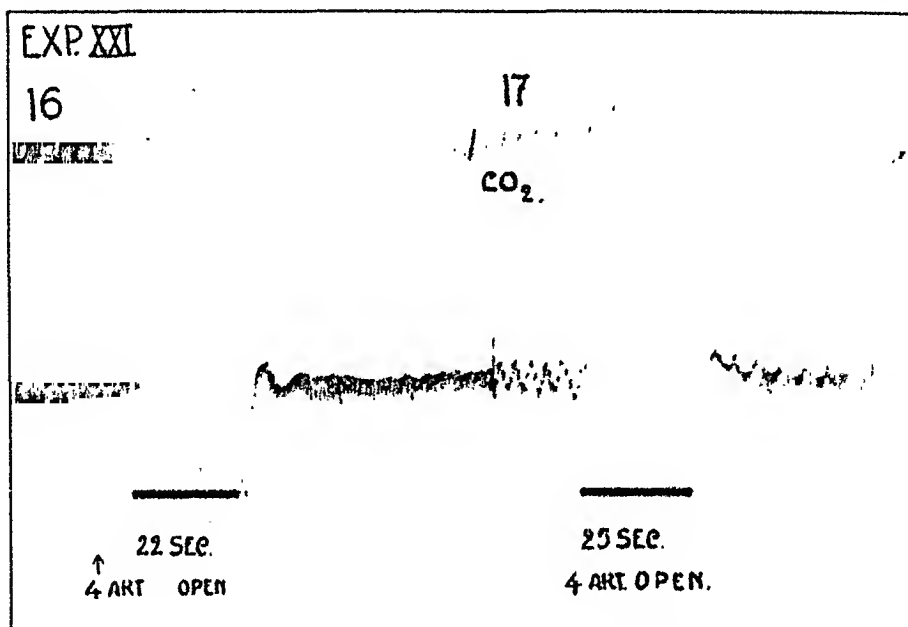


Fig. 12.—Experiment XXI. Dog in morphia-pernocton narcosis. All arteries to the brain are open. Inhalation of oxygen has no influence on the period of apnea (16) following cardiac standstill, while inhalation of mixture of oxygen and 5 per cent carbon dioxide makes it disappear (17).

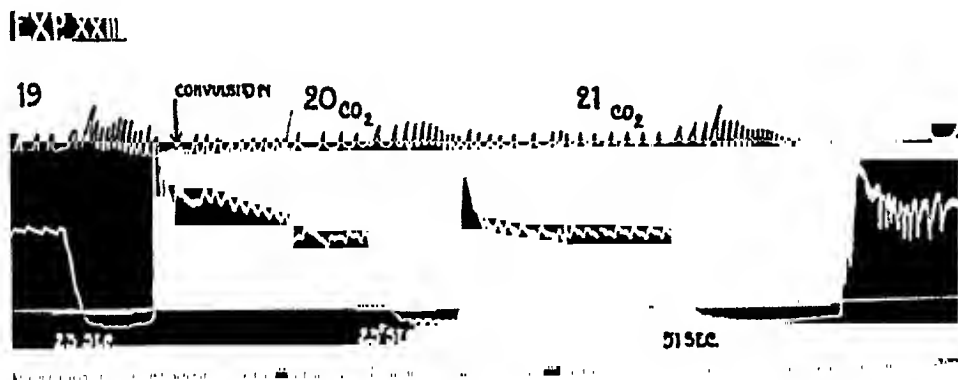


Fig. 13.—Experiment XXIII. Dog in morphia-pernocton narcosis. Asystole for twenty-three seconds during inhalation of oxygen was followed by apnea and mild clonic contractions (19), but asystole for the same period of time during inhalation of oxygen with 5 per cent carbon dioxide was followed neither by apnea nor clonic contractions (20). When asystole lasted for fifty-one seconds during inhalation of oxygen with 5 per cent carbon dioxide, apnea appeared before cardiac contraction commenced (21).

syndrome (Fig. 13). Experiment IV shows that during standstill of the heart hyperventilation and marked loss of carbon dioxide do occur in the blood which comes to rest in the lungs. Experiment III indicates that hyperventilation plays an important rôle in bringing about the period of apnea observed to occur after

recovery of the heart beat. It should be emphasized that the results were not uniform in Experiment III. In most instances, however, the periods of apnea failed to occur during inhalation of oxygen with 5 per cent carbon dioxide. Sometimes reflexes of the carotid sinus apparently played an additional rôle (Fig. 14). In the same experiment a short period of apnea still occurred after bilateral vagot-

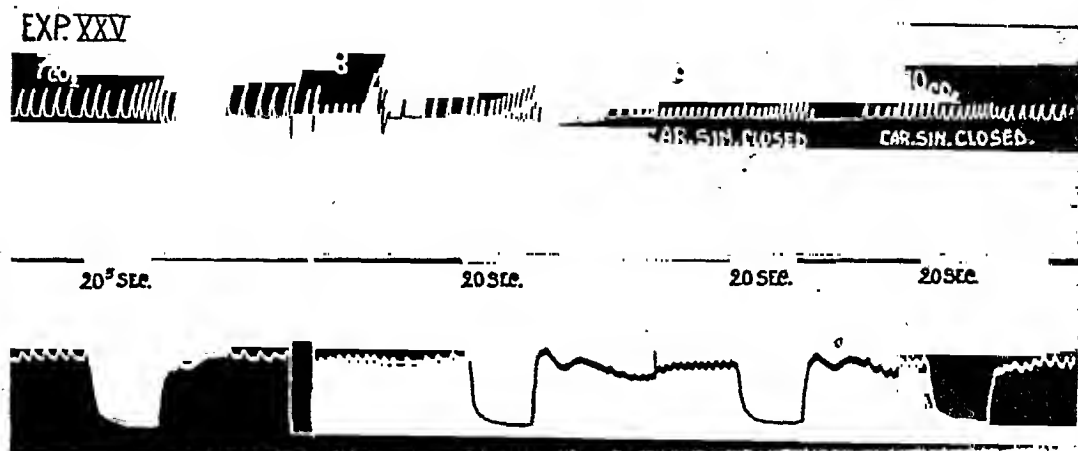


Fig. 14.—Experiment XXV. Dog in morphia-pernocton narcosis. In this experiment asystole during inhalation of oxygen and carbon dioxide, as well as during inhalation of oxygen was followed by apnea (8). After clamping all vessels to and from the carotid sinus, during inhalation of oxygen, asystole was still followed by apnea (9) but inhalation of oxygen and 5 per cent carbon dioxide prevented its appearance (10).

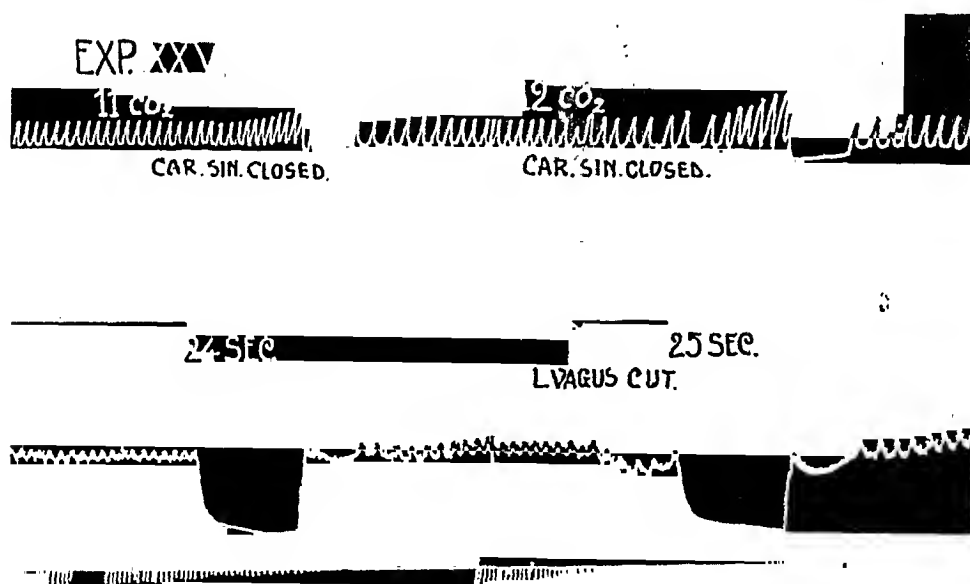


Fig. 15.—Experiment XXV. Continuation of Fig. 14. During occlusion of both carotid sinuses and inhalation of carbon dioxide, a longer period of asystole (twenty-four seconds) was again followed by a small period of apnea (11). Even when bilateral vagotomy was performed in combination with the above procedure, asystole (twenty-five seconds) was still followed by apnea (12).

omy, elimination of both carotid sinuses and inhalation of 5 per cent carbon dioxide mixture (Fig. 15). The reason for apnea was not clear in this instance.

Vagal stimulation for obtaining cardiac asystole had the obvious disadvantage that it did not resemble the cause of the Adams-Stokes attacks in man. It was possible too,

although very improbable, that vagal stimulation of the lungs influenced the phenomena studied. It seemed advisable, therefore, to bring about functional cardiac standstill in another way. Direct faradic stimulation of the heart initiates ventricular fibrillation which may recover spontaneously. The procedure is not useful in dogs, as spontaneous recovery is very rare. In cats, however, periods of ventricular fibrillation of the desired length can readily be induced by short periods of faradic stimulation (one to two seconds). The influence of vagal stimulation during cessation of the circulation is, in this way, eliminated.

Experiment V. It was found that ventricular fibrillation of moderate duration (twenty to thirty seconds) was followed regularly by a period of apnea, but when

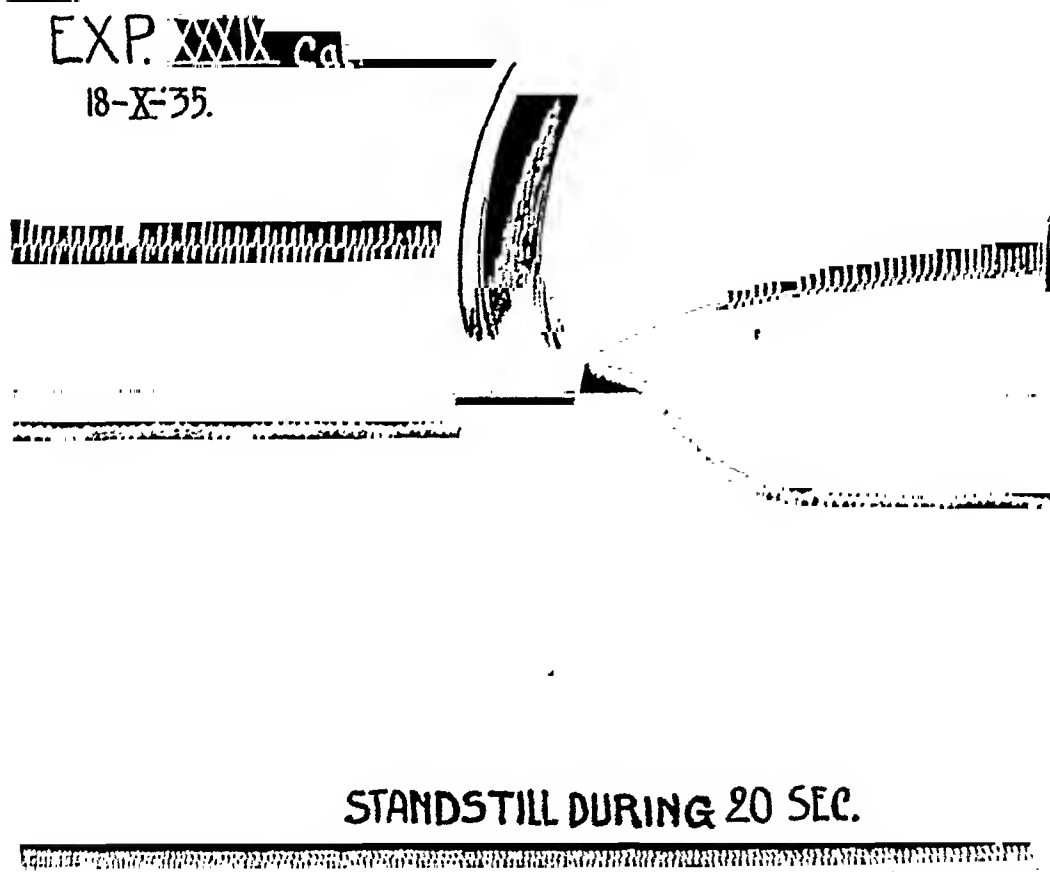


Fig. 16.—Experiment XXXIX. Cat in pernocton narcosis. Direct faradic stimulation of the heart for seventy-two seconds resulted in ventricular fibrillation (proved by electrocardiographic tracings in other experiments). After spontaneous recovery of coordinated ventricular contractions, apnea occurred.

it lasted longer (more than thirty-five to forty seconds) apnea began during the period of fibrillation just as in the experiments in dogs where asystole was produced by vagal stimulation.

Exact analysis of the period of apnea in cats presented greater difficulties than it did in dogs, for two reasons: (1) In each animal only a small number of experiments could be carried out, usually not more than three; (2) the duration of ventricular fibrillation could not be regulated. Spontaneous recovery had to be awaited. In some experiments inhalation of 5 per cent carbon dioxide mixture shortened the period of apnea, but did not make it disappear. A clear statement of its effect on apnea in this type of experiment cannot yet be made. Often slight

clonic cramps were observed during the period of apnea similar to those seen in dogs. Before passing on to the general discussion it appears desirable to point out that the mechanism responsible for cessation of the circulation, i.e., ventricular fibrillation, in these cats was similar to that observed in Case 5.

DISCUSSION

In summarizing the sequence of events which follow transient cessation of the circulation, it becomes plain that no matter what the method used to stop the circulation, either convulsions or apnea alone follow (Table I). In a few of the animal experiments apnea was combined with mild convulsions. The relation between these two different effects requires analysis.

TABLE I

CEREBRAL SYMPTOMS FOLLOWING TRANSIENT CESSATION OF THE CIRCULATION

	APNEA	CONVULSIONS
A. Adams-Stokes syndrome		
Patient 1	0	+
Patient 2—during consciousness	0	+
during coma	+	0
Patient 3	+	0
Patient 5—(ventricular fibrillation)	0	+
B. Syncope by fright or pain in healthy individuals		
Patient 4	0	+
C. Experimental standstill of the heart		
First by faradization of the vagus nerve in dogs	+	±
Second by direct faradic stimulation of the heart	+	±
in cats (ventricular fibrillation)		

1. As it has been shown that the occurrence of hyperventilated blood in the lungs leads necessarily to apnea after the attack, it may be assumed that apnea is also present during convulsions, but that it cannot be clearly observed because of the violent muscular movements.

2. The occurrence of convulsions when hyperventilated blood reaches the brain is, to a large extent, dependent upon the state of the brain and the degree of consciousness. This is demonstrated most clearly in Case 2: convulsions occur after the attacks during consciousness but are absent during coma. The occurrence of convulsions in "healthy" individuals after syncope, and their absence or mildness during narcosis in animals, is additional evidence that the state of consciousness is important. That mild convulsions occur occasionally during narcosis makes analysis difficult. Convulsions could probably be readily reproduced by vagal inhibition of the heart in non-narcotized animals but the experiment is scarcely justified.

It is certain that the convulsions begin at the precise moment that hyperventilated blood reaches the brain. The conclusion is therefore drawn that these convulsions are probably caused by the action of hyperventilated blood with its loss of carbon dioxide and the attendant

alkaline reaction on the brain. Some support of this view can be found in the increase of reflex irritability and the production of epileptic fits known to follow hyperventilation. Inhalation of the oxygen plus 5 per cent carbon dioxide gas mixture should in this case relieve the convulsions. The administration of this mixture during attacks to patients in whom convulsions ordinarily follow the attack will perhaps settle this point. The possibility that sudden excess of oxygen, reaching brain cells that have been anoxic, is responsible for the convulsions, cannot be excluded.

The importance of local hyperventilation of the stagnant blood in the lungs in standstill of the heart has been demonstrated in the preceding observations and experiments. Now in sudden slowing of the circulation, hyperventilation of the blood must also occur if respiration does not diminish. This hyperventilated blood is transported to the respiratory center and if the level of carbon dioxide has been sufficiently reduced apnea will occur. Attacks of Adams-Stokes syndrome are often preceded by slowing of the rate. In the third patient the short periods of apnea which preceded attacks may conceivably be explained by slowing of the circulation. Proof for this tentative explanation cannot be offered.

It is unlikely that periodic breathing of the Cheyne-Stokes type can be explained by this mechanism. In simultaneous records of respiration and electrocardiogram slowing of the rate preceding the apneic phase was not observed. The gradual waxing and waning of respiration in Cheyne-Stokes breathing is, moreover, not seen in the periods of apnea caused by local hyperventilation, where there is an abrupt end and beginning of respiration. In chronic slowing of the circulation, hyperventilation in the lungs is counterbalanced by many factors; but it should be emphasized that slowing of the circulation through the lungs can of itself never lead to anoxemia of the arterial blood.

SUMMARY

1. In patients with complete heart-block and attacks of ventricular asystole, or with ventricular fibrillation, apnea or convulsions were observed to occur *after* the attack.

2. In healthy persons mild convulsions were observed to follow syncope due to emotion.

3. In narcotized animals in which cardiac standstill was induced by vagal inhibition, or ventricular fibrillation was caused by faradic stimulation of the heart, apnea was observed to occur *after* recovery of the heart.

4. Convulsions occurred only during consciousness. They were not observed in individuals in coma or in narcotized animals.

5. It was shown that during cardiac standstill continuance of respiration hyperventilates the blood in the lungs which is transported, on recovery of the heart, throughout the body and the respiratory center. It was furthermore demonstrated in animal experiments that this mechanism is mainly responsible for the period of apnea for, when oxygen and 5 per cent carbon dioxide were inhaled, apnea failed to occur. Carotid sinus reflexes and other mechanisms may, however, occasionally play an additional rôle.

6. Convulsions were therefore ascribed to the action of hyperventilated blood upon the brain. Further analysis was not possible.

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ELECTROCARDIOGRAPHIC CHANGES OCCURRING WITH ALTERATIONS OF POSTURE FROM RECUMBENT TO STANDING POSITIONS

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IN 1935, Leimdörfer¹ observed changes in the T-wave, from positive to isoelectric and to negative coincident with alteration of posture from standing to recumbent. He attributed these electrocardiographic changes to latent and clinically undetectable cardiac disease.

I have found no other references in the literature to electrocardiographic observations on alteration of body posture from recumbent to standing, although many such studies in other postures have been re-

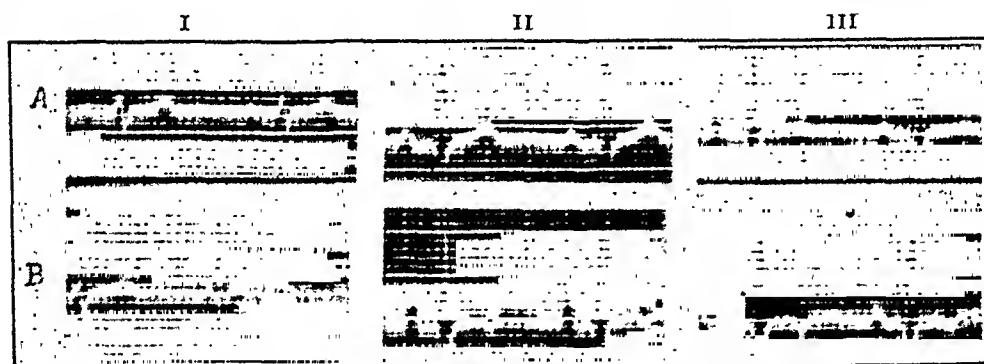


Fig. 1.—Changes in the T-wave in Leads II and III on change in posture. No appreciable changes in the QRS complexes. A, recumbent; B, standing. The electrocardiogram was obtained from a normal heart.

corded. I have therefore carried out such observations in a series of 100 consecutive cases that came to my office. Tracings were taken in the three standard leads with the patient in the dorsal recumbent posture. With the electrodes still connected, the patient was then made to stand up and the tracings were repeated several minutes after adjustment to change in posture. In some cases tracings were also taken with the patient in the sitting posture, supported by a back rest at an angle of about ninety degrees, and with the legs in a horizontal position. In most cases the fourth lead was also employed.

The cases were divided into Group 1, consisting of individuals with normal hearts, and Group 2, consisting of those showing gross cardiac disease. The electrocardiograms were analyzed by calculating the angles of the electrical axes of the QRS complexes and the T-waves, obtained in the various postures. From these, the directions and therefore any rotation of the electrical axes were ascertained. In cases where the

fourth lead was also employed, the differences in the voltage of the various components of the initial and terminal ventricular complexes were employed to gauge any changes that might occur.

RESULTS

The findings bring out very interesting facts which may prove to be of value in the interpretation of the electrocardiogram as an aid in

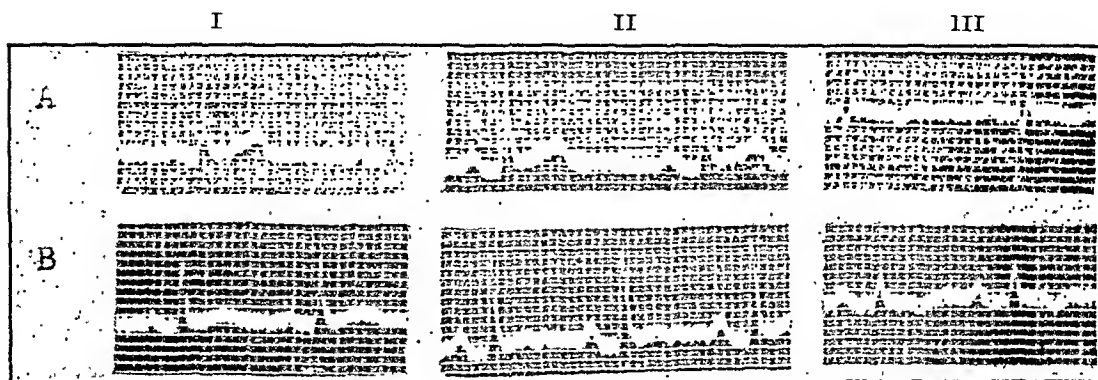


Fig. 2.—Change in T-wave in all leads and some shift in the axis of the QRS complex on alteration of posture. A, sitting; B, standing. Electrocardiogram obtained from a patient exhibiting the anginal syndrome in a mild degree.

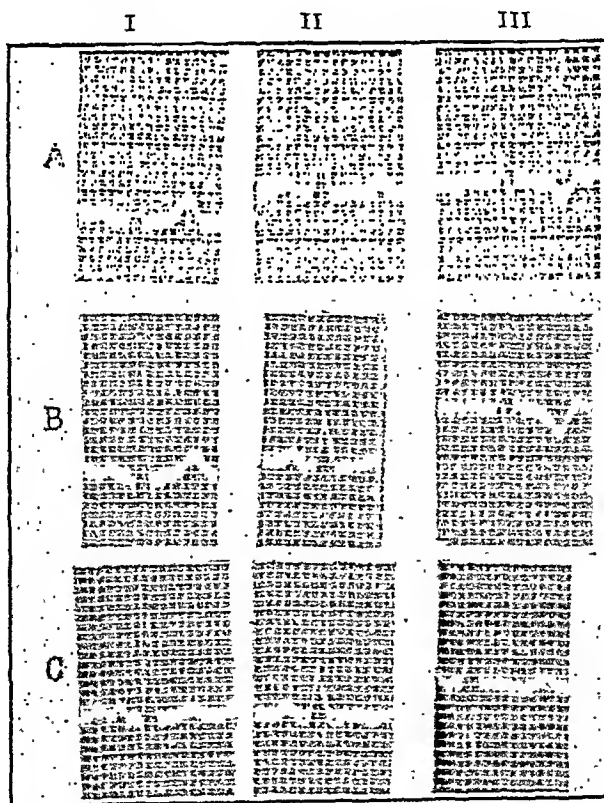


Fig. 3.—Progressive shift of the axis of the QRS complexes and changes in the T-waves on alteration of posture. A, recumbent; B, sitting; C, standing. Case of arteriosclerotic heart disease.

diagnosis. In many patients with perfectly normal hearts, there were definite and distinct changes noted, both in the QRS and in the T-waves, on alteration of posture from the recumbent to the standing, and even

on change from the recumbent to the sitting and sitting to standing position. The changes in some cases were so marked as to make the

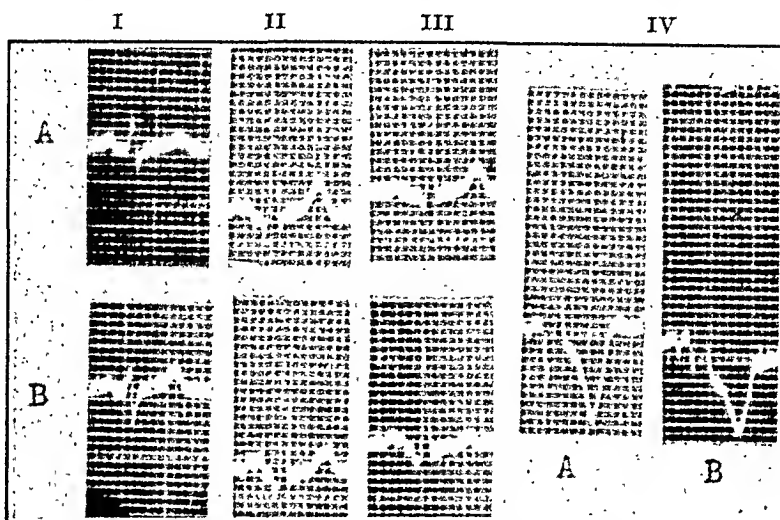


Fig. 4.—Rotation of the electrical axis of the QRS complex to the right and of the T-wave to the left and diminished voltage of the Q- and T-waves in Lead IV on alteration of posture. A, recumbent; B, standing. Case of mitral valvular disease, rheumatic.

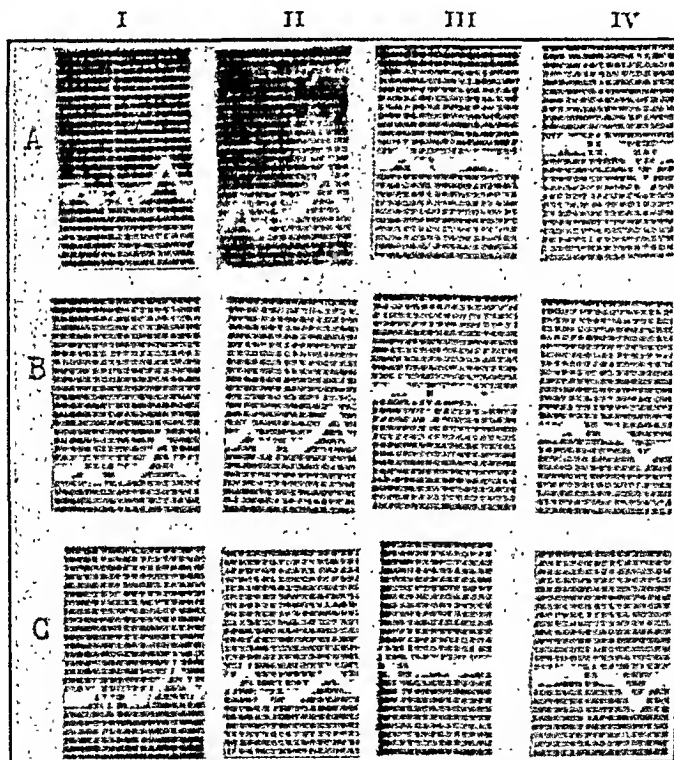


Fig. 5.—To-and-fro shifting of the electrical axis of the QRS complexes and the T-waves on alteration of posture. A, recumbent; B, sitting; C, standing. Case of thyrotoxic heart disease.

electrocardiogram appear abnormal and to lose its identity with those taken in the other postures in the same case. Individuals with abnormal hearts showed no greater changes than those with normal hearts.

In some cases changes occurred only in the T-wave, as shown in Fig. 1. The changes in these cases consisted of diminished voltage, flattening or actual conversion from a positive to a negative phase in one or more leads. This usually occurred in the third lead or in the third and second leads. In other cases there were concomitant changes in the QRS complexes with the T-wave changes, as shown in Fig. 2. Many showed shifting of the electrical axis of the QRS complex in various directions as well as changes in the T-waves producing alterations in their electrical axes, as shown in Figs. 3, 4, and 5. The axis shift of the initial and terminal ventricular complexes occurred either in the same direction or in opposite directions. If in the same direction, the amount of shift was not proportionate. If premature contractions were present, their voltage change was usually different than that of the normal complexes, as shown in Fig. 6.

A summary of the entire series of cases showing the changes of direction of the electrical axes among the normal and diseased hearts is given

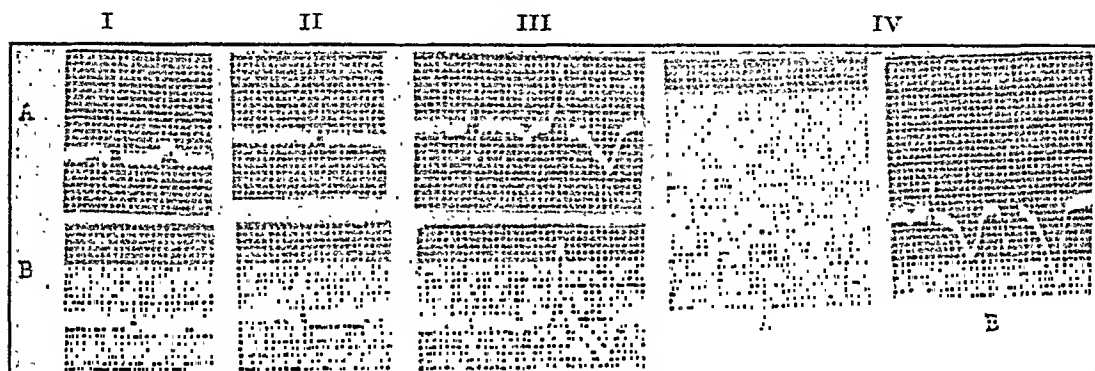


Fig. 6.—Diminished left axis shift of the QRS complex and change in voltage of T-wave with alteration of posture; also changed voltage of the ventricular premature contraction and the QRS complex in Lead IV. A, recumbent; B, standing. Case of hypertensive heart disease.

in Table I. It will be noted that a greater number of cases show shifting of the electrical axis of the QRS complex to the left in diseased hearts than in normal ones. The total number of cases showing any shifting, whether to the left or right, is the same in the normal as in the diseased hearts. Thus the differences in the behaviour of the normal group as compared with the diseased group is merely a difference in the direction of the shift. In the normal heart there is a greater tendency of the electrical axis to shift to the right while in the diseased heart the tendency is to the left. The T-wave, on the other hand, has a greater tendency to have its axis shift to the left in the normal and to the right in the diseased heart, on change from the recumbent to the standing posture. There is definitely a smaller number of cases showing a shift in the electrical axis of the T-wave than of the QRS complex with alteration of posture, in both normal and diseased hearts.

The degrees of the angles of the electrical axes in the three standard leads occurring with alteration of posture in the entire group of 100

cases are recorded in Table II and Fig. 7. Case numbers 1 to 33 represent normal hearts, and 34 to 100, abnormal hearts. The fourth lead changes are also shown. It will be noted that the greatest changes in degree of the angles occur on alteration of posture from the recumbent to the standing. Alteration of posture from recumbent to sitting showed less change while that from sitting to standing, the least. The shift of the electrical axes of the T-waves was less marked than that of the QRS complexes.

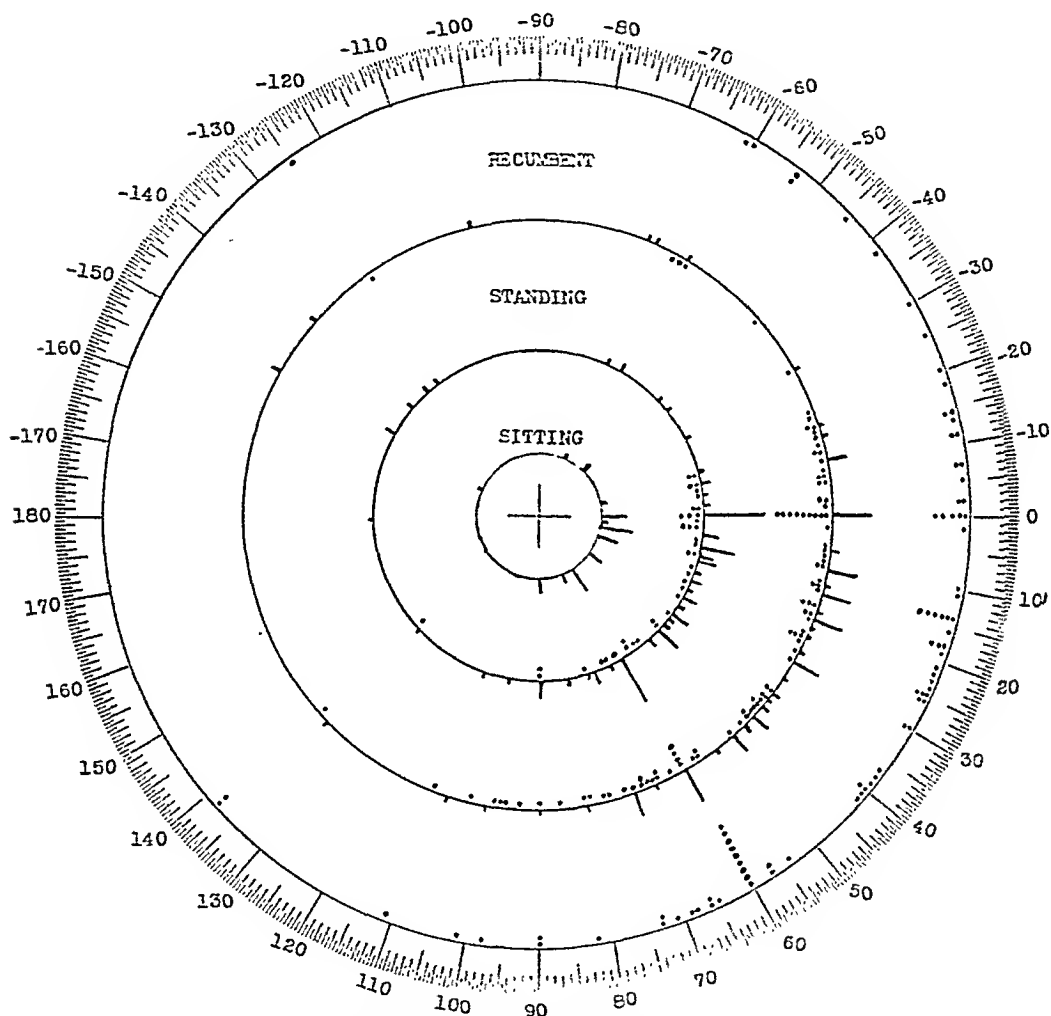


Fig. 7.—Graphic representation of the number of cases showing varying degrees of electrical axis deviation in the recumbent, standing, and sitting postures. Dotted lines represent axes of the QRS complexes, one dot per case. Solid lines represent axes of the T-waves, calibrated on a scale of 0.5 mm. per case.

DISCUSSION

It has been known for many years that changes occur in the electrocardiogram with alterations of posture from the dorsal recumbent to the left or right lateral recumbent and the sitting positions. Also displacement of the heart by pneumothorax, hydrothorax, massive adhesion, and other conditions are known to produce changes. Shifting of the electrical axis did not correspond in many cases with change in the anatomical axis of the heart occurring with alteration of the body posture. Thus, Meek and Wilson,² Nathanson,³ Treiger and Lundy,⁴

TABLE II*

CASE NO.	DEGREE OF ANGLE OF ELECTRICAL AXIS (ANGLE ALPHA)						LEAD IV IN 0.1 MV.					
	QRS			T-WAVE			LYING			SITTING		
	LYING	SITTING	STANDING	LYING	SITTING	STANDING	Q	R	T	Q	R	T
1	60		68	49		60		10	-2			12
2	40		40	44		44						
3	73		73	0		-2			-4			
4	13		76	60		39	5	10				11
5	66		60	16		16						
6	54		49	46		46	5	8				
7	21		39	16		7		4	-6			
8	14		14	71		71						
9	39	43	58	60	60	60		12				
10	71	66	66	60	60	60						
11	57	57	57	60	60	60						
12	57		66	60		60						
13	13	74	80	67	39	60						
14	82		94	71		41						
15	16	4	24	30	0	0	15	7				10
16		0	0		-7	-7						
17		4	8	49	41	41						
18	41		41	11	49	49						
19	42		42	11	11	11	13	11	-11			12
20	24		28	0	0	0		7	-4			8
21	26		26	0		0						
22	60		41	49		11	8	7				6
23	19		21	11		11	12	5				6
24	14	14	-13	23	23	19						
25	-2		-2	44		44	13	7				8
26	38		39	16		16						
27	-14	-14	-14	24	24	24						
28	14		18	43		36	3					
29	25		20	0		0						
30	2	2	10	60	60	30		13	-7			15
31	14		13	0		0	4					
32			25	44		44		19				24
33	-25	-15	-16	44	14	35						

*Case numbers 1 to 33 represent normal hearts.
Case numbers 34 to 100 represent diseased hearts.

Katz and Robinow⁵ and others found that displacement of the heart to the left may in some cases be associated with rotation of the electrical axis to the right, in others to the left and in still others with no rotation. The same was true of displacement to the right. In other words, changes in the electrical axis were not always consistent with the theory of the Einthoven equilateral triangle. In many cases there were merely changes in the voltage without axis shift.

Experimentally, Kountz, Prinzmetal, Pearson, and Koenig⁶ found that the degree of displacement of the heart determined the resultant electrical axis and if the heart was rotated rather than displaced the electrical axis corresponded to the direction of rotation. They believed that electrical axis changes were due to alterations in the relationship of the septum of the heart to the long axis of the body.

It is unlikely that the same conditions occur in clinical cases. It is possible that in individuals with hearts of unequal size alterations in the body posture may result in unequal displacement of the heart. Given a group of similar cases, as in our series such a condition is not likely to occur. Furthermore it is not conceivable that alterations of body posture from sitting to standing would change the anatomical axis of the heart to a sufficient degree to affect the electrical vectors. The explanation of such changes cannot therefore be made on the basis of change of the position of the heart.

An explanation of these changes is to be had perhaps in the work of Katz and his coworkers. Katz and Korey⁷ insulated various areas of the heart in dogs and found that the lungs and large systemic vessels were poor conductors of the electric current elaborated in the heart while the solid structures in contact with the heart were good conductors. They felt that changes in the electrocardiogram with alterations of posture were due largely to reorientation of various parts of the heart with good and poor conductors which alter the current coming from the heart. In other words they believed that not all portions of the heart share equally in giving rise to an electric vector, and that the changes in the electric field with alterations of posture are not due to reorientation in the three dimensions of the resultant vector. It is the contact of various parts of the heart with different adjacent conducting media that determines the resultant electrocardiogram. "Electrical axis" or "shift in the electrical axis" are misnomers, according to their conception. They considered the area of cardiac dullness, the diaphragm and the lower part of the posterior muscle mass of the vertebral column to be good conductors. Later, Katz and his associates⁸ further demonstrated the importance of the electrical properties of the tissues adjacent to the heart in determining the type of electrical current set up in the heart.

These experimental observations would explain not only the changes in the electrocardiogram with alterations of posture from reclining to

standing but also the changes observed on alteration of posture from the upright sitting to standing, in which cases the electrical vectors, according to the Einthoven triangle, should be the same. Slight displacement of the abdominal contents and changes in the position of the body structures in the two postures would conceivably alter the conducting media adjacent to the heart and therefore the resultant electrocardiogram.

The changes in the appearance of the T-wave independent of the QRS complex are due to differences in the mode of spread and retreat of the current. According to Lewis⁹ the spread of excitation is rapid and is controlled mainly by the Purkinje system, while the period of activation, comprising the full excitatory state and recovery, is much longer and concerns the mass of ventricular muscle. Changes in the relationship of the various portions of the ventricular muscle with the adjacent conducting structures may conceivably result in changed registration of the electromotive force, incident to activation and retreat in the localized portions of the muscle.

From the observations and considerations presented in this paper it is readily seen that changes in the appearance of the T-wave with alteration of posture from standing to recumbent do not indicate latent or inactive cardiac disease as claimed by Leimdörfer.¹ On the contrary, in the interpretation of any electrocardiogram it is very important to know the position in which it was obtained before any significance may be attached to its complexes, especially to the T-waves. This is particularly true when two electrocardiograms of the same patient are compared to ascertain if any changes have occurred in the heart muscle. Unless we are sure that the tracings were obtained in identically similar postures, any changes observed may be considered due to change in posture rather than to changes in the myocardial state.

Although the number of cases in this series is not great enough from which to draw conclusions, it appears that in the normal heart there is a greater tendency to a shift of the electrical axis of the QRS complex to the right and of the T-wave to the left on change in posture from the recumbent to the standing. In abnormal hearts, the shifts are in the opposite directions. This might prove to be of help in differentiating the normal from the abnormal heart. It does not indicate, however, disease of the heart muscle, but most likely disproportion in the sizes of the right and left ventricles in the two types of hearts, with the resultant differences in the reorientation of the two chambers to their environment caused by alteration of posture.

SUMMARY AND CONCLUSIONS

Electrocardiographic studies were carried out on 100 cases on alteration of posture from the dorsal recumbent to standing and sitting positions. The three conventional leads and the fourth lead were used.

Definite changes in the appearance of the QRS and the T-waves were observed in many cases on these alterations of posture. The changes in the T-wave usually occurred independently or were different than those expected from the preceding QRS complexes. In some cases the changes were so marked as to make the electrocardiogram appear abnormal and to lose its identity with those taken in the other postures. The changes occurred as frequently in normal as in diseased hearts. In normal hearts there was a greater tendency for the electrical axis of the QRS complex to shift to the right and of the T-wave to the left, while in the diseased heart the tendency was of shifting to the left for the QRS and to the right for the T-wave. This fact might prove to be of help in differentiating the normal from the diseased heart. It does not indicate, however, disease of the heart muscle but probably a disproportion in the sizes of the left and right ventricles in the two types of hearts with the resultant differences in reorientation of the two chambers to their changed environment caused by alteration of posture from recumbency to standing.

In most cases the changes did not conform to the theory of the Einthoven equilateral triangle for the shift in the electrical axis was not always as predicted from the supposed shift of the anatomical axis. The phenomenon may be explained on the theory that there occurs a change in contact of the adjacent conducting media with different portions of the heart on alteration of body posture, producing variation in conduction.

The observations demonstrate the importance of knowing the posture in which a tracing was taken before any pathological significance is applied to it. They also may prove to be of value in determining the relative sizes of the chambers of the heart.

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THE USE OF SODIUM NITRITE FOR TESTING THE FLEXIBILITY OF THE PERIPHERAL VASCULAR BED*

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IN THE study of the different types and stages of peripheral vascular disease, an important problem arises from the standpoint of prognosis and therapy namely: how much of the terminal vascular bed is closed by spasm or by organic disease? The production of fever with typhoid vaccine, the raising of body temperature by heat or by preventing heat loss, the application of direct heat to the affected limb, and the release of vasomotor control by peripheral nerve block or by spinal anesthesia have been extensively used to determine the patency of the terminal vascular bed. Their use has in the main been to select cases suitable for sympathectomy; and the rise in skin temperatures obtained was interpreted as a release of local, central, or reflectoric vascular spasm.

It seems more logical, however, as was first suggested by Shaw¹ to regard these tests as indicators of the reserve capacity of the vascular bed. It is true that this capacity may be diminished by vasospastic phenomena of Raynaud's or Buerger's disease, but frequently parts of the terminal vascular bed are obliterated by organic processes and the vasodilatation following any of these procedures simply indicates the residual reserve, one which is not called into play in the resting stage but functions during activity. The estimation of this collateral reserve thus becomes an important diagnostic and prognostic measure, not only in regard to the feasibility of a sympathectomy but as an aid in determining whether conservative devices, such as suction and pressure² or intermittent venous hyperemia,³ offer any reasonable possibility for improvement.

THE TEST

An oscillometric curve is determined at the ankle or the wrist. A Pachon oscillometer is sufficient for the purpose but for an easier demonstration of the test we are showing records obtained with a self-registering device. In these determinations a single cuff was used. The patient lies in a horizontal position with the extremity exposed to its root. The room temperature is preferably between 70° and 80° F., although the action of sodium nitrite on the peripheral vessels is independent of environmental temperature. One cubic centimeter of a 4 per cent solution of sodium nitrite (0.04 gm.) is given intravenously at a slow rate of speed. The solution must be either prepared immediately before use or put up in dark ampules filled close to the top in order to prevent oxidation of the solution, which rapidly takes place

*From the Neurocirculatory Clinic, Department of Surgery, University of Illinois. College of Medicine. Aided by a grant for graduate research of the University of Illinois.

in the presence of oxygen.* The maximal vasodilatation occurs between ten and fifteen minutes after the injection, although the effect lasts at least for one hour (Fig. 1). After a great many tests, we take the second reading ten minutes after the injection and compare the two oscillographic curves. The patient may then get up and leave.

With this dosage we have not observed untoward symptoms in a single instance, although more than 100 patients have been subjected to this test.

THE MECHANISM OF ACTION

Sodium nitrite has been used for many years for the reduction of blood pressure, accomplished by changes in peripheral circulation. A searching inquiry as to the exact localization of vascular relaxation has been made recently by Soma Weiss and his coworkers.^{4, 5, 6} They have come to the conclusion that the drug acts by decreasing the tone of the venocapillary bed, thereby producing a pooling of blood on the venous side of the circulation, which can be accentuated by assuming upright posture. These authors also state that the arterioles are not dilated, in fact, there occurs an arteriolar constriction as a response to the falling blood pressure. Blood flow is thus decreased, but the capacity of the vascular bed to hold blood must be larger. The arterioles maintain their tone and are susceptible to reflex vasomotor responses during the action of sodium nitrite.

As will be shown in some of our graphs, the marked increase in oscillographic curves may be present with practically no change in systolic and diastolic blood pressure, which can only be explained by a persistent tonus of the arterioles. It must be remembered though that our dose is much smaller and yet the action of the drug is more rapid because of the intravenous administration. Weiss and his associates used three to four times as much sodium nitrite orally. The circulatory collapse induced by them would call for an arteriolar constriction. What we seem to measure then, with our larger spikes and with the shift of our oscillographic curves to the right, is an increased filling of the venocapillary bed and a decrease in resistance in that area. As this filling is dependent on the patency of the small arteries and arterioles, we feel that the rapidity with which the venous pool forms still remains an index of arterial flow, provided the dose is so selected that a marked fall in blood pressure does not occur. When that occurs, the secondary arteriolar constriction will so cut down blood flow that the individual pulse volumes diminish and the test does not inform us as to the reserve capacity of the vascular bed. It is for this reason that the selection of the small dose of 0.04 gm. ($\frac{2}{3}$ of a grain) is important. That arteriolar dilatation can be induced by nitrites is shown by the initial flushing of the head and face, which occurs after the inhalation of amyl nitrite.† It seems to us then, that for a proper evaluation of the capacity of the peripheral vascular bed, such measures must be selected which avoid a fall in blood pressure. Even so, the element of reflex vasoconstriction to maintain this blood pressure will have to be considered.

OBSERVATIONS

We have introduced this test in our neurocirculatory clinic as a routine measure and have taken several hundred readings. We wish only to

*We gratefully acknowledge the help of Dr. Wm. C. Welker, Professor of Physiological Chemistry of the University of Illinois, in the preparation of a stable solution, which does not contain nitrates after a few weeks in the ampules. To obtain uniform results, however, it is better to dissolve the powder in a few cubic centimeters of normal salt solution and boil it in a spoon just before use.

†The temperature of cutaneous flares, produced by intradermal injections of histamine, can be raised by the intravenous administration of sodium nitrite. It is difficult to explain this finding without assuming that arteriolar dilatation has taken place.

show a few graphs to illustrate the value of the drug and to compare it with other known methods employed to produce vasodilatation.

Figure 1 illustrates the effect of the drug in a normal, young individual. It will be noted that the effect is at its peak at ten and fifteen

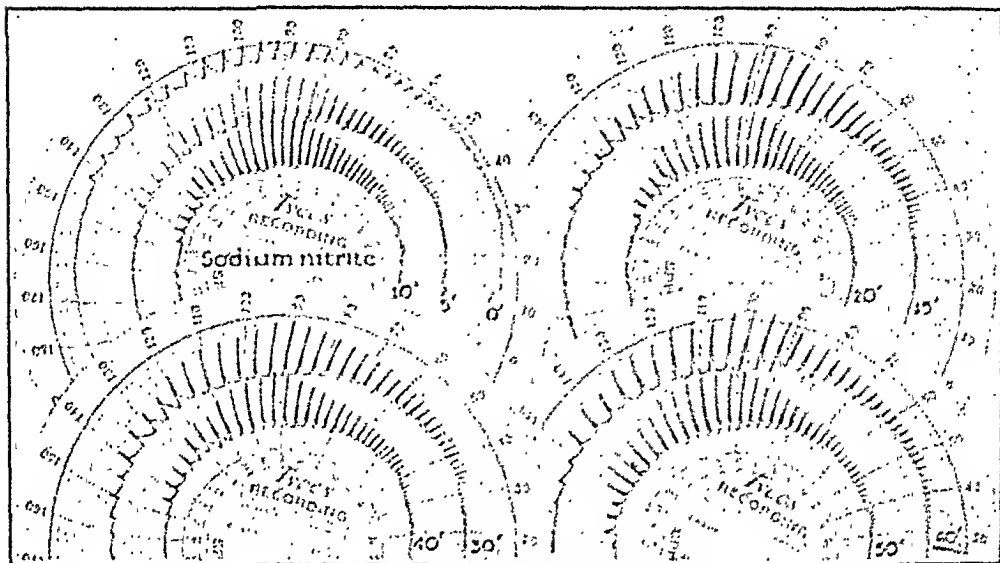


Fig. 1.—Oscillometric records in a young individual with normal circulation. The measurements in this and the following graphs were made with a single cuff at the ankle. Following a reading obtained at zero, 1 c.c. of a 4 per cent solution of freshly prepared sodium nitrite solution was injected. Note the greatly enlarged pulse volumes. The shift of these spikes toward the right half of the chart indicates a lowering of peripheral resistance. It is most marked at fifteen minutes, where the spikes between 80 and 70 millimeters of mercury are the largest. The effect is still present at the end of one hour.

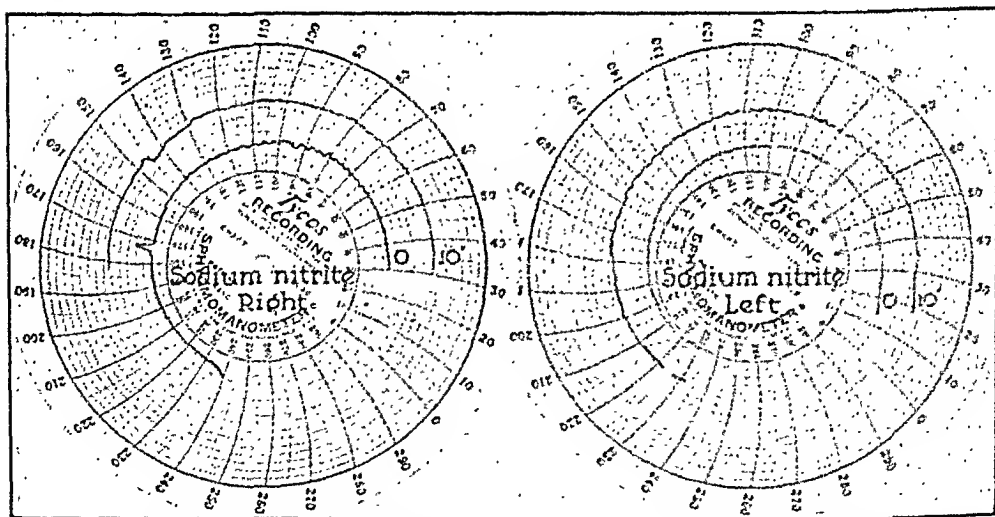


Fig. 2.—A fifty-six-year-old male with arteriosclerosis of both lower extremities. Oscillometric curves before and after sodium nitrite was given. There is a slight shift of the curve to the right, which showed less oscillation to the drug. Curiously enough, the right gave a better response

minutes, but that it is still present at the end of one hour. In this it differs from amyl nitrite, which acts very abruptly and produces a sudden fall in blood pressure, the maximum fall being caught usually

between thirty and forty-five seconds after inhalation. Although we used amyl nitrite in a few of our hypertensive patients to demonstrate the flexibility of the diastolic level, we have now abandoned its use because of the disagreeable and perhaps not entirely harmless symptoms.

In obliterating arteriosclerosis the flat or absent oscillometric curve is hardly influenced by the intravenous administration of sodium nitrite (Fig. 2). The same is true in thromboangiitis obliterans with extensive

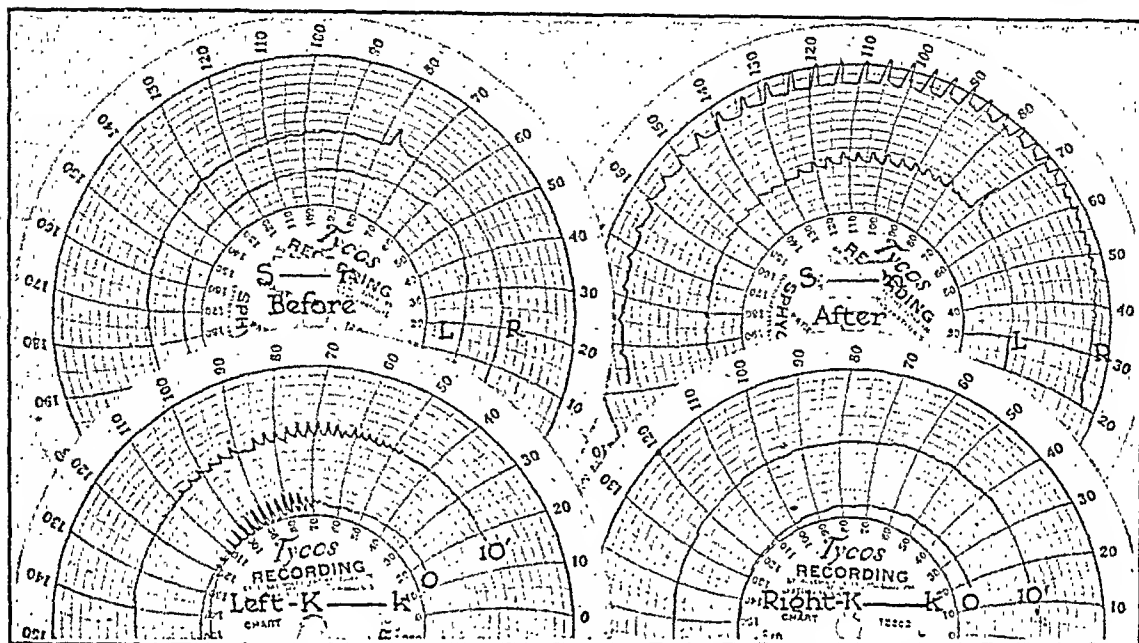


Fig. 3.—Two patients suffering from Buerger's disease. In the case of Sn., the left lower extremity shows much smaller vascular capacity than the right. In the case of Kk., the right lower extremity did not respond at all. Both patients showed a far greater clinical improvement after sympathectomy on the side which responded better to sodium nitrite.

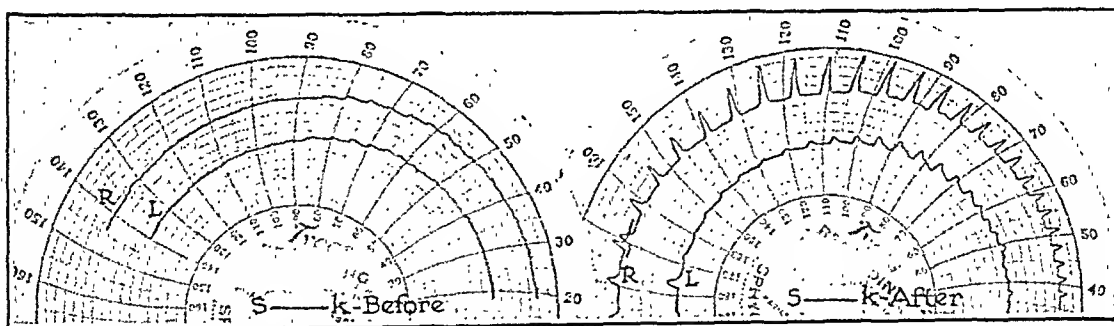


Fig. 4.—A twenty-three-year-old student, showing a marked difference in response to sodium nitrite. Clinical diagnosis was Buerger's disease, with impalpable pedal arteries of both feet. Following sodium nitrite both vessels of the right foot became palpable. The vasospasm in the right foot is here clearly demonstrated. The left lower extremity is in a more advanced stage of the disease.

organic damage in the absence of superimposed spasm. In the earlier cases of Buerger's disease, however, the response may be marked (Fig. 3). When both lower extremities, or all four extremities are involved, the test may give evidence of different grades of involvement (Fig. 4). We have come to rely with increasing assurance on this test in regard to the benefit to be derived from a sympathectomy. The extremity with a

poor response to sodium nitrite will not react as favorably as the one with a good response. This does not mean that the lack of good response contraindicates sympathectomy. The benefits of this operation in Buerger's disease have been discussed by one of us elsewhere,⁷ but the

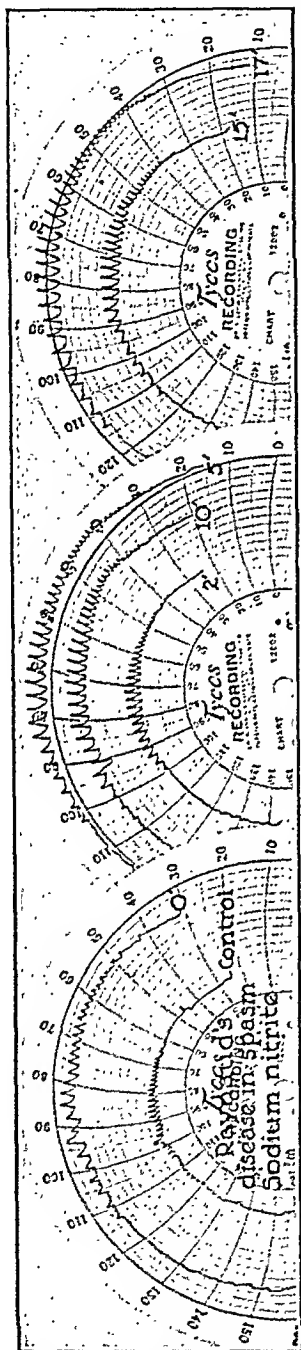


Fig. 5.—A. M., A thirty-one-year-old woman suffering from Raynaud's disease. The first reading was obtained during spasm as a control curve. At zero, the needle was inserted. The last reading at seventeen minutes seemed to give the maximum response. The pallor and cyanosis of the fingers disappeared at ten minutes. The test demonstrates the lack of marked structural change in the terminal vascular bed. She was subjected to sympathectomy.

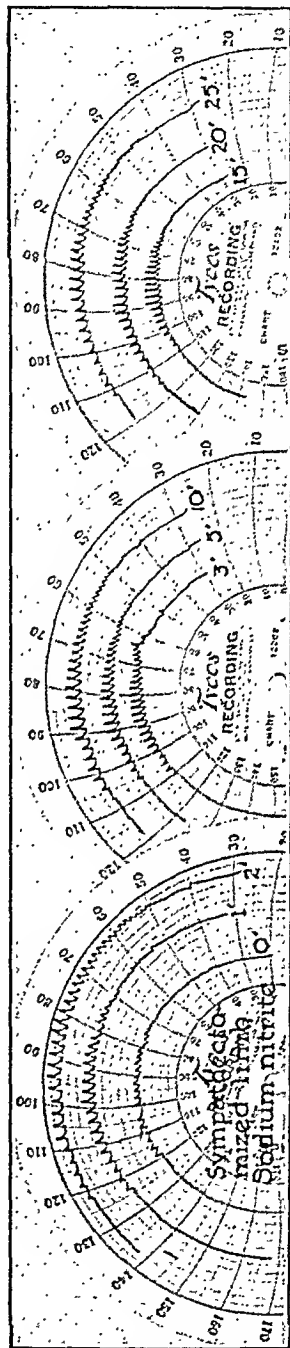


Fig. 6.—A forty-five-year-old male in whom preanginal thoracic sympathectomy was performed three months previously for a persistent chronic ulceration due presumably to a defect in the spinal cord. Good response of the sympathectomized vessel. Oscillations diminish after ten minutes.

test gives a good indication as to what may be expected. In Raynaud's disease, the presence or absence of structural damage can be demonstrated by this test. Thus in Fig. 5 it was possible to release a vasospastic attack by nitrite and show that the opening of the minute vessels is readily accomplished in this case.

Sympathectomized or completely denervated extremities show normal response to this test (Fig. 6). Following exposure to heat, sodium nitrite gives evidence of a further increase in capacity (Fig. 7). Compared with papaverine, sodium nitrite acts much more rapidly, although the action of papaverine is more prolonged. At ten minutes the action of sodium nitrite compares favorably with the action of papaverine at thirty minutes (Fig. 8).

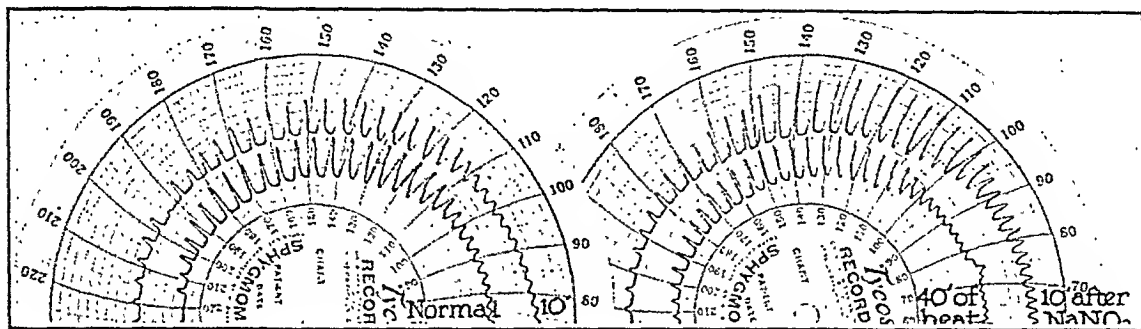


Fig. 7.—The response of a preheated extremity to sodium nitrite. After forty minutes of direct heat at 110° in a thermostatically controlled cradle, vasodilatation is still possible with the use of sodium nitrite.

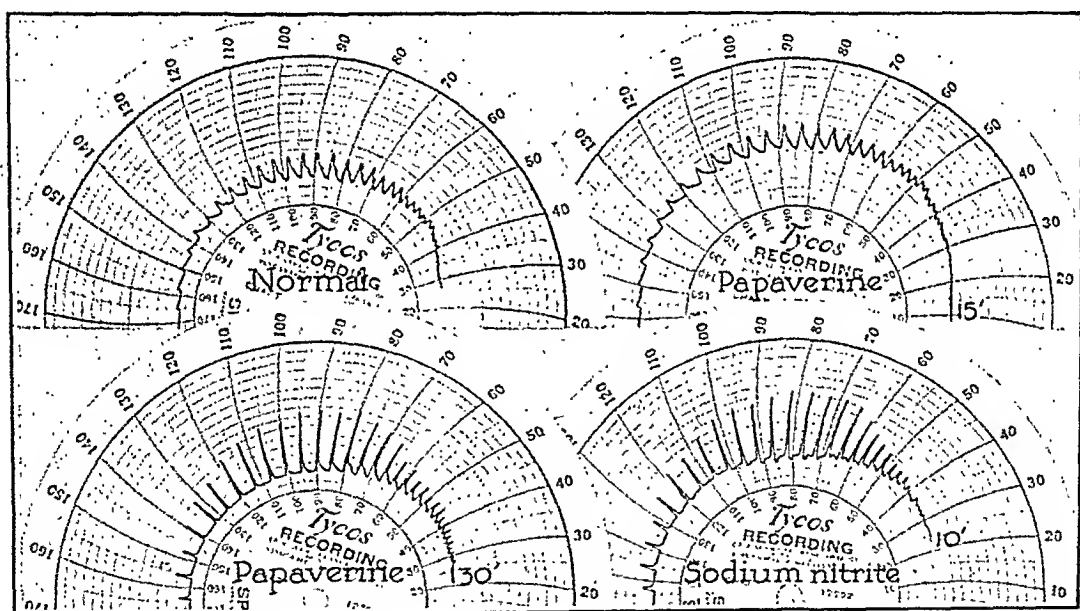


Fig. 8.—Comparative effect of sodium nitrite and papaverine. The maximum vasodilatation after the intravenous use of papaverine was attained at thirty minutes. A corresponding effect could be obtained in ten minutes with sodium nitrite. At fifteen minutes, papaverine has hardly started to act.

DISCUSSION

With a simple and, as far as our experience goes, quite harmless test, it is possible to obtain a graphic picture of the capacity of the peripheral vascular bed. This capacity will naturally depend on the age of the patient, on environmental temperature, metabolic requirements, and amount of spasm, but chiefly on organic vascular damage involving the terminal vascular bed. Thus we believe that it has prognostic value, as the chances of reopening the terminal bed are notoriously poor, and it is

in this group, as Herrmann and Reid have pointed out, that suction and pressure treatments are least effective.²

The graphs indicate that peripheral vasodilatation may be readily induced with a small amount of sodium nitrite without producing a significant fall in blood pressure. Whether the drug acts primarily on the veno-capillary bed or, as we believe, produces a diffuse relaxation of the terminal bed with secondary arteriolar constriction in order to maintain blood pressure does not affect the usefulness of this method. Obviously if the dose is so selected that larger drops of blood pressure are avoided, the diminution of blood flow, as a consequence of reflex arteriolar constriction, will not be a disturbing factor. The dose is so selected that even patients with marked hypertension will not experience a significant fall in blood pressure.

SUMMARY

For a test of the capacity of the terminal vascular bed, a simple ambulatory test is described. It consists of a preliminary determination of an oseillometric curve, followed by the intravenous administration of 0.04 gm. ($\frac{1}{2}$ grain) of freshly dissolved sodium nitrite solution. From ten to fifteen minutes later a second oseillometric curve is determined. The comparison of the two curves as to the height of oscillations and the shift of the spikes toward lower levels of pressure give a graphic illustration of peripheral vascular capacity.

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THE ELECTROGRAM OF CARDIAC MUSCLE: AN ANALYSIS WHICH EXPLAINS THE REGRESSION OR T DEFLECTION

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I

EVER since the discovery that an electrical response is associated with the activity of certain tissues, physiologists have been interested in ascertaining the origin and nature of these currents. While these two subjects are closely associated, they are not identical. In the former belongs the effort to discover the physicochemical reactions in tissue that produce the electrical energy, in the latter, the endeavor to ascertain the character of the currents produced, their distribution and association with the other manifestations of activity. To the general physiologist the origin of the electrical response has been the subject of greater interest while the nature of the currents has been investigated only as a means to this end. But now that electrocardiography has come to play an important rôle in clinical medicine, a clear description of the electrical events which take place in a single cardiac muscle fiber as a result of activation is a matter of practical importance apart from any light it may throw upon the origin of these currents. Since this investigation sheds no direct light on the origin of action currents the history of that subject will not be discussed. Meanwhile it is desirable to consider briefly the state of knowledge of their nature—at least so far as heart muscle is concerned.

The experiments upon which this knowledge is based fall into two categories, those performed in moist air and those in which the tissue is in situ or is immersed in a vessel containing physiological salt solution which serves as an extensive conducting medium. However the experiments were performed, provided only that the muscle was uninjured, the response obtained consisted of two parts, a rapid primary deflection and a slower secondary or T deflection.

In the first group of experiments it was invariably found that when one electrode connected with a galvanometer was on active and the other on resting muscle, the active muscle was negative with respect to the resting. Consequently, the first theory to gain general credence was the so-called negativity hypothesis or theory of distributed potential differences. According to this theory active muscle becomes negatively charged (Fig. 1A). While anyone familiar with electrical phenomena

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from the physical point of view would have found many reasons for considering the theory untenable, it explained fairly satisfactorily the early experiments performed on simple muscle strips suspended in moist air.

It was not until Lewis¹ began his investigations of the electrocardiogram that this theory was seriously questioned. After making a critical study of the spread of the impulse over the heart with the organ in situ he discovered that he could not explain his observations on the assumption that all active muscle was negative relative to resting, for he found that the sign of the galvanometric deflection depended only upon the direction in which the impulse was at the moment spreading and not on the location of the mass of active muscle as a whole with respect to the mass of resting muscle. He put forward an hypothesis, therefore, which he called the theory of limited potential differences. The view was that only the muscle which had just become active was relatively negative and that only the inactive muscle immediately adjacent was relatively positive (Fig. 1B). This idea adequately explained all his experimental observations. Lewis did not push the idea beyond his immediate needs, however, and did not make use of it in his explanation of the secondary or T deflection. It is unwise to conclude what an author's view would have been about a situation which he did not discuss unless such a view follows unequivocally from definite statements in his published work. No effort is made, therefore, to carry Lewis's theory further than he himself carried it. For a time there seems to have been little interest in the subject. But in 1927, Craib,² working with cold-blooded and mammalian hearts immersed in large baths of physiological saline solution, made an accurate study of the electrical field surrounding active heart muscle, and demonstrated, though not for the first time, the necessity of applying the laws which govern the distribution of potential in volume conductors* to this problem. Because he found while making these studies that he could assume the source of potential difference during systole to be a doublet† he proposed a doublet theory for the nature of the electrical manifestation of muscular activity. According to this theory, at the moment of activation,

*By a volume conductor is meant an extensive tridimensional conducting medium. A jar of physiological saline solution, or the body of a patient or an animal is a conductor of this sort. Certain of the early investigators, notably Waller and Einthoven, understood that it was necessary to apply the laws which govern the distribution of potential in volume conductors when dealing with the heart in situ, and whatever simplifying assumptions they made they were careful to justify. Later investigators for the most part, however, did not realize the necessity of the application of these laws. The report of Wilson, Wolshart, and Herrmann³ in 1926 was probably the first in more recent years to call attention to the fact that the body must be regarded as a volume conductor.

†A doublet is a positive and negative pole of equal strength located very close together, strictly speaking infinitely close together, i.e., a potential difference with magnitude and direction located at a point. The conception is a mathematical fiction devised to facilitate the application of mathematics to the solution of electrical problems. A potential difference which extends over a very small space behaves, of course, under certain circumstances, like a doublet; any potential difference can be represented by a combination of doublets. Craib may not have appreciated the fictitious character of doublets and the equivalence of a train of doublets to a potential difference extending over a space.

doublets develop in the tissue and endure there for a brief period. Later, as activity subsides, doublets of opposite sign appear and last a somewhat longer time (Fig. 1C). Results of experiments on muscle strips could be accurately predicted from this theory whereas predictions on the basis of the old negativity hypothesis could not be verified.

Finally, Wilson, Macleod, and Barker^{3, 4} made an extensive study of the laws which govern the distribution of potential in volume conductors and their application to the problems of electrophysiology. They treated the subject more generally than Craib had done and reduced their analyses to mathematical form. In this way they were able to plot curves that should be obtained if the conditions assumed prevailed and to compare these with electrograms obtained by experiment. There was very close agreement between their theoretical and their actual curve. Their conclusion was, "whatever may be the origin of the elec-

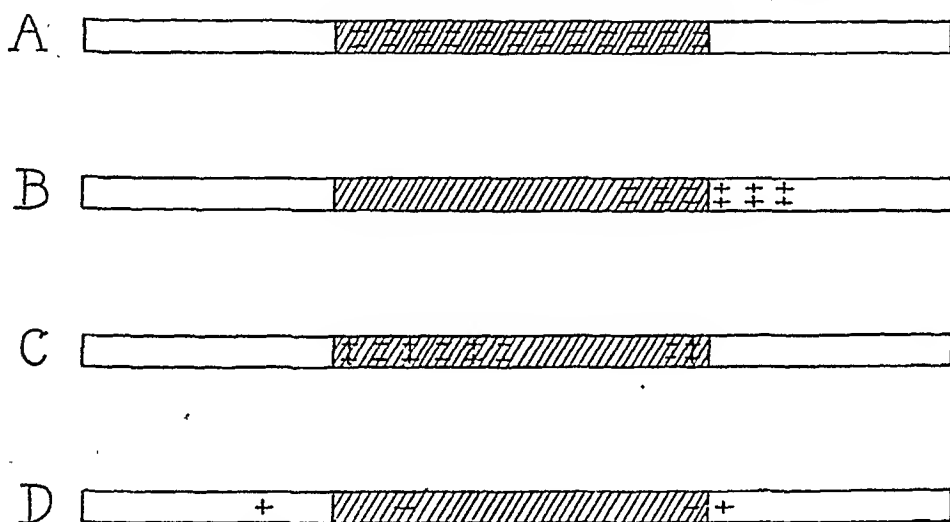


Fig. 1.—A diagrammatic representation is given of the various theories of the nature of the electrical manifestations of activity in cardiac muscle. In each case activity is spreading from left to right. The active region is shaded.

A. The negativity hypothesis. The entire mass of active muscle is represented as being negatively charged. The inactive muscle is neutral.

B. The theory of limited potential differences (Lewis). A small region where the muscle has just become active is negative and the immediately adjacent resting muscle is positive.

C. The doublet theory (Craib). As muscle becomes active it becomes the seat of doublets whose positive element is toward the resting muscle. When muscle regresses from the active state, it gives rise to doublets of opposite polarity.

D. Bipolar theory (Wilson, Macleod, Barker). Ahead of the advancing boundary between resting and active muscle is a positive pole and behind it a negative pole. Across the retreating boundary is a potential difference of reversed polarity but in this case the poles are farther apart.

tric currents associated with the excitation wave, these currents are similar to those which would be produced if the crest of the excitation wave were immediately preceded by a source (positive pole) and followed by a sink (negative pole)." They suggested also that the secondary or T process is caused by a sink followed by a source, but that in this case the poles are farther apart (Fig. 1D).

The first (negativity) theory in the light of present knowledge is untenable. The difficulties with it have been pointed out by Craib² and

by Wilson, Macleod, and Barker³ and need not be dealt with at length, except to point out the nature of the fallacy involved. If a strip of muscle AD (Fig. 2) surrounded by moist air is stimulated at A , its active (shaded) portion is negative with respect to its resting portion. In other words, so long as the boundary between active and resting muscle (X) is between B and C , an electrode at B is negative with respect to one at C . The inference drawn was that this result signified that active muscle was negatively charged because inactive muscle was neutral (Fig. 1A). This, however, is only one of two possible explanations. An equally satisfactory and more probable one is that a potential difference exists at the boundary X between active and resting muscle (Fig. 1D as contrasted with Fig. 1A). Under the circumstances just described, with the muscle suspended in moist air, if a potential difference existed at X , the strip BX would act as an extension of the electrode B and, therefore, seem to be negative, and XC as an extension of C , and seem positive. In the case of a linear conductor, which a mus-

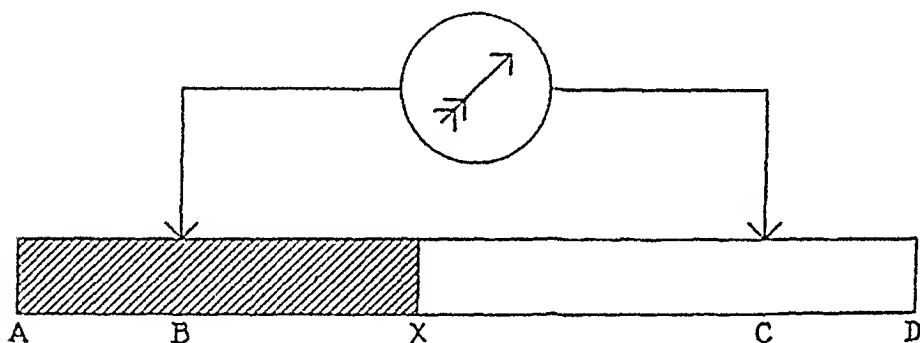


Fig. 2.

cle strip suspended in air closely approximates, it is impossible to differentiate between the two explanations. If the muscle strip were immersed in a sufficiently large bath of saline solution, however, it could be ascertained which explanation is correct, that is, whether the entire mass of active muscle behaves as an extensive negative pole and the entire mass of resting muscle as an extensive positive pole, or whether there seems to be a localized positive and negative pole close together in the region of transition X . The propounders of the last three theories (Fig. 1, B , C , D) have done such experiments and have found the second situation to represent the facts. The three are not dissimilar. Each may in a sense be regarded as an extension and clarification of the preceding.

Lewis explained that his theory of limited potential difference was vague. Nevertheless he demonstrated that the excitation wave is preceded by a positive and followed by a negative region, and that both are of small extent. His failure to offer an explanation of the secondary or T deflection in terms of his theory was its greatest omission.

Craib's doublet theory explained consistently both QRS and T, but was purely qualitative and predicted little more than the sign of the deflections. In the case of the secondary (T) deflection his predictions were furthermore not well borne out by the experimental curves.

Wilson, Macleod, and Barker were more precise in their concepts, and their deductions were expressed in mathematical form so that they were able to predict the shape of the primary deflection with considerable nicety and to demonstrate the significance of the various inflections of the curve. This made it possible to ascertain from the recorded curve a fairly precise description of the electrical process which produced it. They did not attempt to predict the form of the T-wave in direct leads but were able to show by an indirect method that it bore a quantitative relationship to the QRS deflection and was produced by electrical forces of opposite sign.^{4, 5} In a different way each theory has demonstrated that as the excitation wave spreads, it is accompanied by a positive and a negative region each of limited dimensions. The way in which each has pictured the behavior of the electric forces is different, but the differences are superficial, and all are in agreement as to the fundamental nature of the process. Both Craib, and Wilson, Macleod, and Barker have indicated that the secondary or T deflection is probably produced by forces of opposite sign to those that cause the QRS, and that it has to do with the recovery from the active states. But the nature of this process is still far from clear. The object of this research is to describe intimately the concepts of activity in general and the electric phenomena which accompany it, to relate the one to the other and thereby to explain more satisfactorily the nature of the secondary (T) deflection.*

II

This investigation deals primarily with an explanation of the secondary or T deflection. But since it makes use of a new method of analysis, it seems best for the sake of clarity, to deal briefly with the electrical process as a whole.

The ideal experiment for a study of this kind is one in which the physical circumstances are sufficiently well understood and sufficiently simple so that potential changes occurring in a given segment of active tissue can be easily and unequivocally inferred from the record obtained. As has been mentioned, certain information can be gained from experiments in which appropriate tissue is immersed in an extensive conductor

*The work of Eyster, Maresh, and Krasno (Am. J. Physiol. 110: 422, 1934) and Krasno, Eyster, and Maaske (Ibid. 114: 119, 1935) has not been discussed in this paper because their work deals with the potential changes in the heart as a whole as judged by indirect leads rather than the electrical events occurring in a single fiber. These authors have made use of a doublet concept but the doublets which they assume are the resultants of all the potential differences existing anywhere in the heart at a given moment. Theirs clearly is a different concept from the one used here where doublets are used to explain the potential differences existing in single muscle fibers. For these reasons the work of the authors mentioned requires no detailed analysis and comparison with the discussion in this paper. This excellent work will be reviewed in a more appropriate connection.

(a saline bath) that is not forthcoming from experiments performed with preparations suspended in air. There is a distinct disadvantage, furthermore, in placing both electrodes on the tissue being studied, since it is then impossible to tell whether a given deflection is produced by a positive effect at one electrode or a negative effect at the other. As Wilson, Macleod, and Barker³ showed, this difficulty can be avoided by placing one electrode, the exploring electrode, on the tissue under observation, and the other, the indifferent electrode, in the conducting medium at a sufficient distance from the first so that potential differences arising in the active tissue will produce undetectable, because so small, changes in potential in it. The record then describes the potential changes occurring at the point in the active tissue upon which the exploring electrode has been placed. It is, in addition, necessary to know the configuration of the muscle and the way in which the active process passes over it. While a long narrow strip of tissue in which impulses spread from one end to the other would be ideal, it is not practicable to cut such a strip from the heart since it is especially necessary to avoid the complication of electrical effects attributable to injury.

In the auricle of the Louisiana bullfrog, *Rana catesbiana*, the impulse spreads in such a way that the conditions on its anterior surface approximate those in a simple strip of muscle. The impulse arises in the sinus venosus (Fig. 3A, *SV*) and spreads in the auricle from *A* toward *B*. If this anterior portion of the auricle were flattened out its shape would resemble Fig. 3B. At a given moment the division between active and resting muscle might occupy the position of the dotted line. The point *X* indicates the position of the exploring electrode. This arrangement approximates the situation which Wilson, Macleod, and Barker designate as "parallel excitation"² (Fig. 3C). They have shown that the electrogram under these circumstances differs only quantitatively from one produced in a narrow strip.

The impulse arising in *SV* spreads to the ventricle also over the posterior auricular wall on the dorsal aspect of the heart. The potentials produced in this bit of muscle are small and sufficiently distant from the exploring electrode so that their effect is negligible.

In performing an experiment the animal was first pithed to prevent muscular twitching. The chest and pericardium were then opened and in some experiments heart-block was produced by pulling tight a ligature laid around the A-V groove. Since it was necessary to approximate the conditions of an extensive uniform conductor, good contact with all the surrounding tissues was maintained by filling the body cavity with saline solution when necessary. At the site where the exploring electrode was to be placed a small patch of the epicardium was dissected off without injuring the underlying muscle. A small exudation of fibrin then caused the electrode, which consisted of a piece of

thread protruding from the end of a silver tube, to adhere to the muscle without slipping during contraction. The indifferent electrode, a strip of silver, was placed beneath the skin of the hind leg.

Since the resistance of the exploring electrode was of necessity high, a single stage direct current amplifier was used in conjunction with the string galvanometer. The maximum gain of this amplifier was approximately 10. It had, however, to be stable and more than usually "quiet" because of the extreme sensitivity of the recording instrument. The sensitivities actually employed were deflections of 1 to 2 cm. per millivolt. Figure 3A is a diagram of the arrangement in a typical experiment.

When the exploring electrode was placed midway between *A* and *B* (Fig. 3A) the curve obtained was like the recorded curve of Fig. 10C. It may be considered to consist of two parts, a primary deflection which is rapid and diphasic (positive-negative) and a secondary deflection

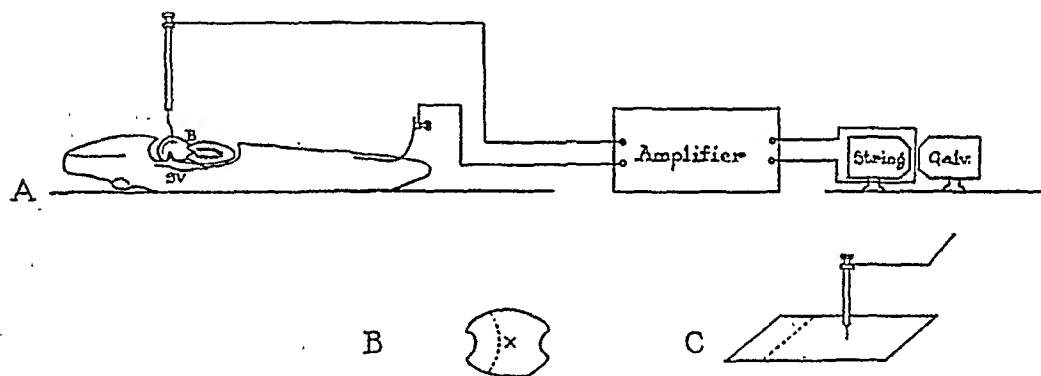


Fig. 3.—A. A schematic arrangement is shown of the method of obtaining electrograms from the uninjured auricle of the frog.

SV = sinus venosus.

A = junction of anterior wall of auricle with sinus venosus.

B = junction of anterior wall of auricle with ventricle.

B. This illustrates the approximate shape of the anterior wall of the auricle. The dotted line represents the position of junction between active and resting muscle at a given moment.

X is the position of electrode.

C. A uniform sheet of muscle is shown in which activity is spreading from left to right. The dotted line indicates the position of the boundary between resting and active muscle at a given moment. This figure illustrates what Wilson, Macleod, and Barker refer to as "parallel excitation."

which is slower and monophasic (positive). An approximately isoelectric period separates these two deflections. The rapid primary deflection of this electrogram corresponds to the QRS group of the electrocardiogram and the secondary deflection to the T-wave.

When the exploring electrode is placed near the auriculoventricular junction the curve obtained is seen in Fig. 11C. This curve differs from the preceding in that the positive phase of the primary deflection is much larger and the negative phase smaller. The portion of the curve separating the primary and secondary deflections is above the isoelectric line, and the secondary deflection is smaller. Finally, if the exploring electrode is placed nearer the sino-auricular junction, the elec-

trogram obtained (Fig. 12C) differs from the one obtained from the central region in an opposite way from the one just described. The positive phase of the primary deflection is smaller and the negative phase larger, the portion of the curve which separates primary and secondary deflections is below the isoelectric line and the secondary deflection is larger.

To explain the form of these curves it is first necessary to return to a consideration of certain theoretical matters.

III

Before considering the electrical events which take place in a muscle fiber during activity it will make for clarity if the general process of activation is described.

If a long muscle fiber (Fig. 4A) is stimulated at the left end, the excitation process spreads toward the right at a certain velocity which may be designated V_e . When it reaches each minute muscle element such as x_1 , x_2 this element becomes active and remains so for a time (T) and then returns to the resting state. During the time (T) that x_1 , x_2 is in some stage of activity, the excitation process will have progressed along the fiber. The distance traveled will be TV_e . At any instant after stimulation a length of muscle (L) equal to TV_e is, therefore, in some stage of activity. That is what is meant by the length of the active process. The total time during which the segment is active (T) may be divided into three parts, the period during which its activity is increasing (T_1), the period during which it is fully active (T_2), and the period during which its activity is regressing (T_3). During these intervals T_1 , T_2 , T_3 the excitation process will have traveled the distances $T_1 V_e$ (AB , Fig. 4A), $T_2 V_e$ (BC , Fig. 4A), and $T_3 V_e$ (CD , Fig. 4A). These are, respectively, the lengths of the stages of increasing, full, and decreasing activity. Consequently, that portion of a muscle which at any moment is active may be represented as consisting of three parts, a region where activity is increasing (AB , Fig. 4A), a region whose activity is fully developed (BC , Fig. 4B), and a region where activity is regressing (CD , Fig. 4B). During activation a tripartite process of this kind may be pictured as passing along the muscle at the velocity V_e . In the discussion which follows, therefore, the excitation process will be represented as in Fig. 4B. A knowledge of the actual values of T_1 , T_2 and T_3 and V_e constitutes a fairly accurate description of the excitation process. How these are ascertained from a recorded curve will be related in a subsequent report. In this discussion, arbitrary and appropriate values have been assigned to them.

V_e as has been said is the velocity of excitation. This (velocity of excitation) is equal to the velocity of the progress of complete recovery, V_r , if T is the same for every muscle segment. In other words, the

velocity of the right end of the shaded area (Fig. 4A) is equal to the velocity of the left end. If T were to become progressively shorter, however, from left to right, V_r would be greater than V_e , for the length of the active process would be shortening as it progresses; and if T were to become progressively longer from left to right, V_r would be less than V_e , for the process would be lengthening as it progresses. If a uniform fiber is in a uniform environment, however, V_e will be uniform, T will be the same for each element, and V_e will equal V_r . It is these simple circumstances which are assumed to be present in the analyses which follow.

The electrical events accompanying activity may now be described. There is good experimental support for the belief^{2, 3} that a potential difference exists at the junction between active and resting muscle, and that this potential difference is such that the positive pole is toward the resting muscle. Since active muscle must in some way differ from resting muscle, and since at the junction between any two substances that

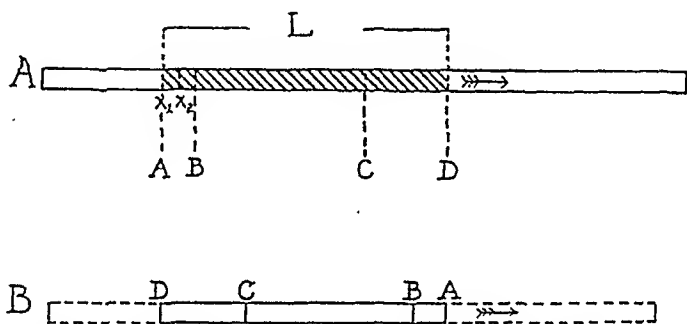


Fig. 4.—A. A muscle strip is stimulated at the left end. The shaded area represents the extent to which the excitation process spread during the time that the muscle in x_1x_2 was in some state of activity.

AB indicates the distance traveled by the front of the active process while activity was increasing in x_1x_2 .

BC indicates the distance traveled by the front of the active process while activity was full in x_1x_2 .

CD indicates the distance traveled by the front of the active process while activity was regressing in x_1x_2 .

B. The tripartite process of activation which is traveling along a muscle strip. The muscle from A to B is increasing in activity; from B to C is fully active; and from C to D is decreasing in activity.

differ from each other chemically or physically, a potential difference may exist, it is probable that in the present case the potential difference occurs because of the difference in composition between active and resting muscle. In the sense that the transition from resting to active muscle constitutes a change in phase, the action current may be considered as resulting from a phase boundary potential. What the ionic mechanism may be, whereby this potential difference is produced, is for the present irrelevant.

A long muscle fiber has been stimulated at the left end and that portion of it which is at the moment active is shaded (Fig. 5). The depth of the shading roughly represents the degree of activity. For convenience the active portion has been divided into small equal segments.

The transition from resting to active muscle at *A* is represented as being abrupt, but that in the reverse direction, in the region *BC*, as taking place in four steps. If the assumption which has been made is correct, a potential difference exists across the boundary *A*, such that its forward looking aspect is positive and its backward looking aspect negative. Across any boundary between *A* and *B* no potential difference exists, however, for the constitution of the muscle on one side is precisely the same as on the other, both fully active. In the case of the boundary at *B*, however, the muscle to the left is slightly less active, than that to the right. Consequently, a potential difference should occur here of smaller magnitude than that at *A*, and of opposite direction. A similar situation exists at each of the segment boundaries in this region, including the one at *C*. The sum of all these potential differences must, of course, be equal in magnitude to the single one at *A*, for one transition is sim-



Fig. 5.—A diagram representing a muscle strip is shown in which the active process is progressing toward the right. The shaded area is the active portion at a given moment. The depth of the shading roughly indicates the degree of activity.

A indicates junction of resting and active muscle.

BC indicates region of decreasing activity.

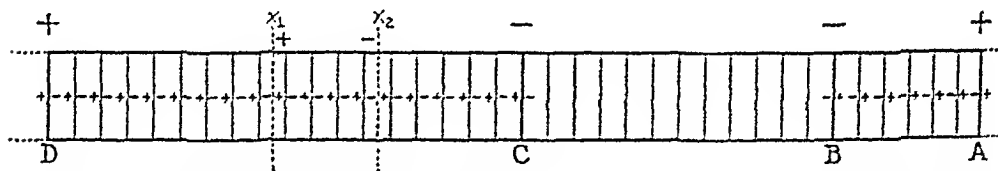


Fig. 6.—A muscle strip is shown in which the active process is progressing toward the right. The active region is divided into small segments. Each is supposed to be in a uniform state of activity throughout its extent. In the region *AB* activity is increasing and each successive segment is more active than its neighbor to the right. In the region *CD* each segment is less active than its neighbor to the right. A potential difference exists between every two adjacent segments if their states of activity are different. In the transitional regions trains of doublets thus arise. These trains are equivalent to a positive and negative pole separated by their length. The total change in potential is the same for both transitions. Thus a given length of muscle x_1x_2 contains a smaller proportion of the total if it is in the region *CD* as depleted than if it were in the region *AB*.

ply the reverse of the other. A transition from resting to active muscle, or vice versa, in reality does not occur abruptly or even in a series of distinct stages, but gradually. In other words, if the number of segments in the region *BC* were greatly increased, the facts would be more correctly represented. In this case each individual potential difference would be less, for the sum must remain the same. In similar fashion, instead of an abrupt transition at *A*, a gradual one of short duration (in many short steps) would represent the course of events more accurately.

Since the number of segments in the transitional regions may be increased without limit, thus approximating the gradual transition with

any desired degree of accuracy, and since a doublet is defined as a positive and a negative charge infinitely close together, muscle in the transitional state may be considered to be the seat of a train of doublets (Fig. 6). It is well known that such a train is equivalent, furthermore, to a single positive and a single negative pole located at either end of the train (Fig. 6). This leads to a generalization of importance, namely, that any bit of muscle, such as x_1 , x_2 (Fig. 6) in the transitional state may be considered to have a positive pole located at its less active and a negative pole at its more active end.

As has been pointed out (Fig. 4B) the active process may be graphically represented as a rectangle divided into three parts corresponding to the phases of increasing activity, full activity, and decreasing activity

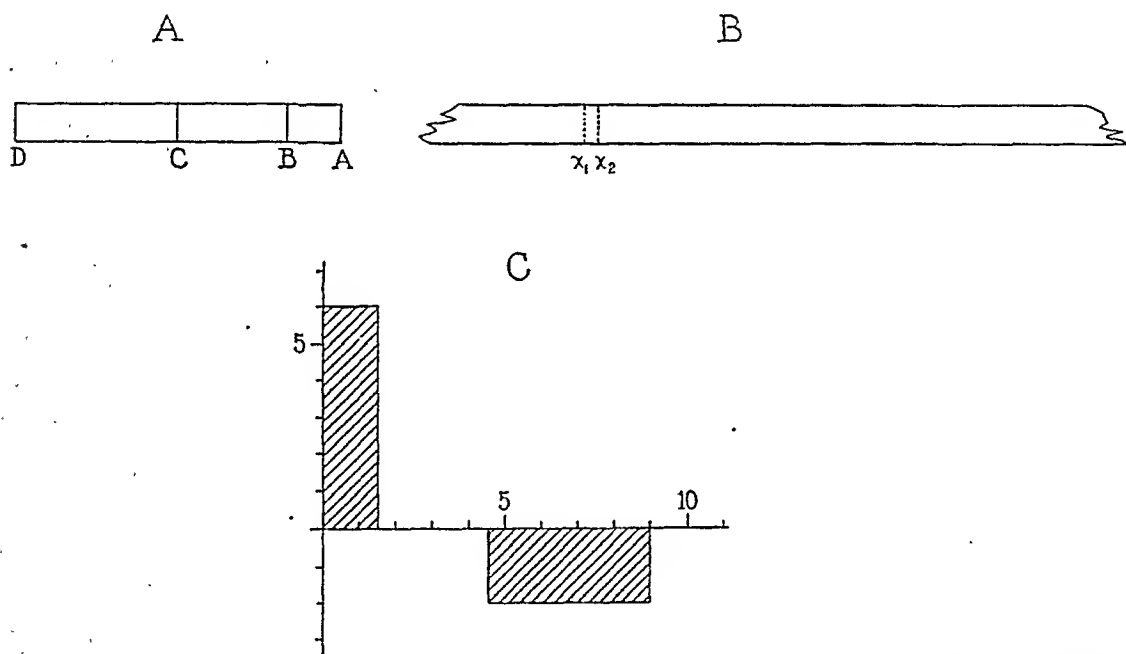


Fig. 7.—A diagram is shown indicating how the process of activation passes over a muscle strip.

A is the process of activation schematically represented.

AB is the stage of increasing activity.

BC is the stage of full activity.

CD is the stage of decreasing activity.

B. Muscle fiber over which the active process A is to pass. $x_1 x_2$ is small segment of muscle whose electrical activity is plotted in C.

C is a graph illustrating the electrical phenomena attendant upon the activation and recovery of $x_1 x_2$. The abscissas are arbitrary units of time and the ordinates appropriate units of potential.

(Figs. 6 and 7A). Since the same change in state, and therefore the same change in potential, is accomplished in the region AB as in the region CD , it must follow that a given short length of muscle, such as x_1 , x_2 (Figs. 6 and 7B), will contain a greater proportion of the total potential difference existing between resting and active muscle when it is in a region where activity is increasing than when in a region where activity is decreasing. The magnitude of the potential difference existing in x_1 , x_2 during increasing activity is, furthermore, as much greater than that during decreasing activity as AB is shorter than CD .

On the basis of this analysis it is possible to illustrate graphically the the electrical events taking place in a small segment of muscle such as x_1, x_2 during activation and recovery (Fig. 7B). While activity is increasing in the region x_1, x_2 the muscle near x_1 is more active than that near x_2 and the segment is consequently the source of a potential difference whose negative pole is at x_1 and whose positive pole is at x_2 . This magnitude is plotted above the axis of abscissas and is given the arbitrary value of 6 (Fig. 7C). Its duration is equal to the duration of the phase of increasing activity. In other words, the electrical activity of x_1, x_2 during the phase of increasing activity is represented by a rectangle whose height is 6 and whose width is equal to AB . While the muscle throughout x_1, x_2 is fully active, no potential difference exists within these confines, so for a period equal in length to BC there is no quantity to be represented. But when the muscle in x_1, x_2 begins to decrease in activity, a potential difference again develops and persists for a period equal in length to CD . During this period the muscle in the vicinity of x_1 is less active than that in the vicinity of x_2 , so that a

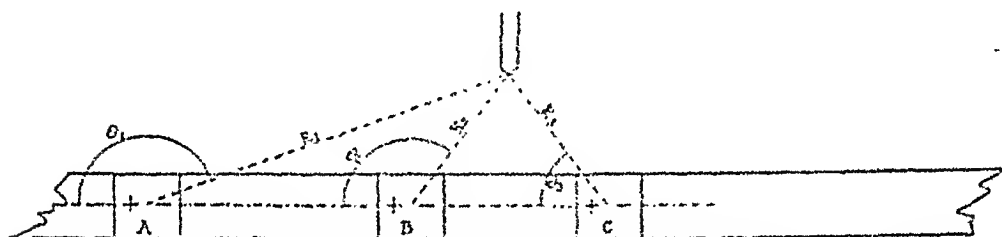


Fig. 8.—The effect is shown of variously placed doublets upon the electrode. A has less effect than B but both effects are negative. The effect of C is equal in magnitude to that of B, but positive.

positive pole will exist at x_1 and a negative one at x_2 . Since the potential difference is opposite to that present during increasing activity, it is plotted below the axis of abscissas. A rectangle results, therefore, one-third as tall and three times as long as the one representing the electrical activity during the phase of increasing activity for CD is three times as long as AB . Before proceeding to the consideration of an actual experiment, another matter must be considered.

An exploring electrode is now represented in relation to the long muscle fiber (Fig. 8). For reasons previously pointed out, it is unnecessary to consider the potential changes of the indifferent electrode (the one at a distance from the active tissue). Since the muscle is immersed in an extensive conduction medium of uniform conductivity, the law³

$$(E = \frac{\mu \cos \theta}{R^2}) \text{ applies, where } E \text{ is the effect upon the electrode}$$

produced by any given dipole, R the distance of the electrode from the center of the dipole and θ the angle between the line from the tip of the electrode to the center of the dipole and the positive end of the axis of the dipole.

This equation expresses the obvious fact that any potential difference anywhere in the medium has an effect upon the electrode, that the more distant it is the less its effect and, furthermore, that its orientation with respect to the tip of the electrode also has an effect. When the positive element is closer (Fig. 8A) the effect is positive; when the negative is

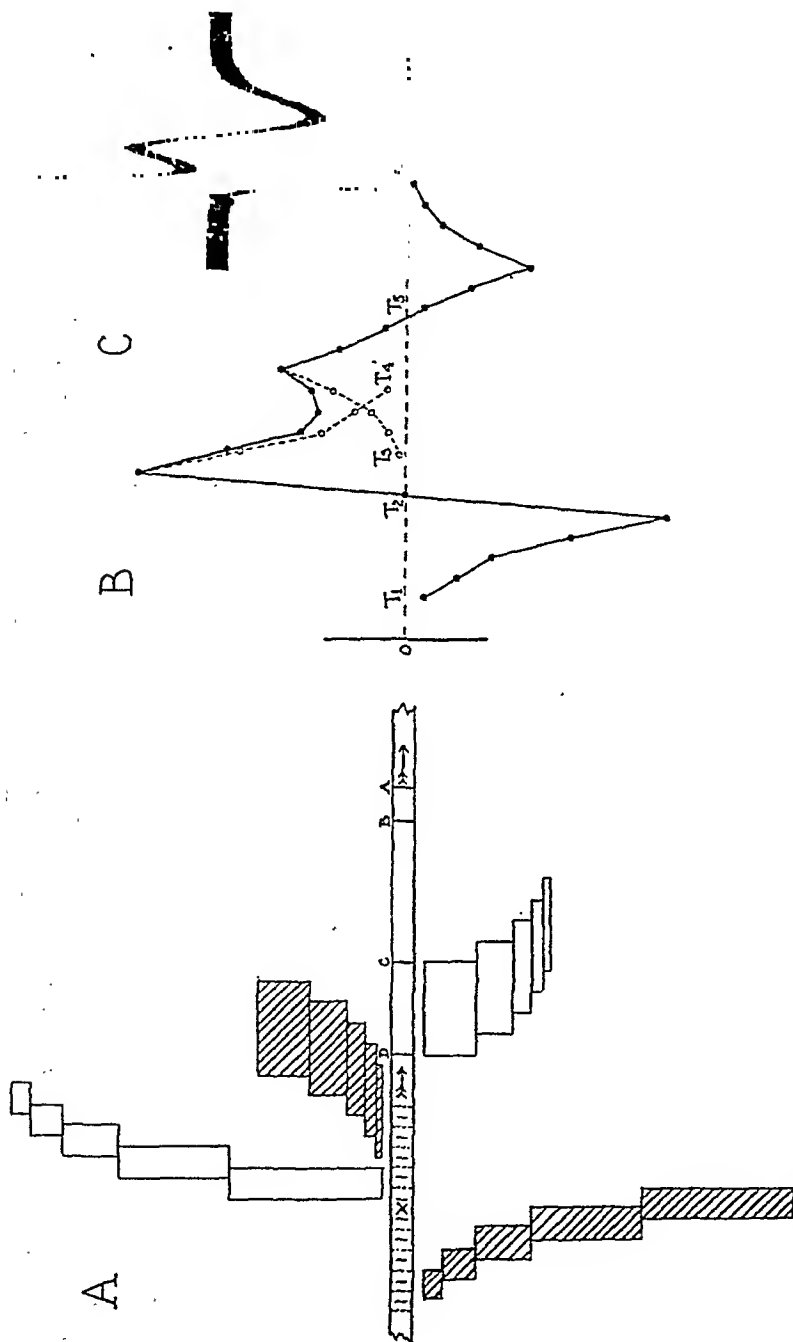


Fig. 9.—A is a plot of the electrical effects of each of ten muscle segments, five on either side of an electrode which is located one unit of distance toward the reader from X. *ABCD* is the excitation process; *AB* the stage of increasing activity, *BC* the stage of full activity, and *CD* the stage of decreasing activity.
B is a graph of the resultant electrical effects for each moment of time during the passage of the excitation process over the ten muscle segments represented in A—i.e., a synthetic electrogram. The dotted line starting at T_1 is a graph of the electrical effects of the regression of activity in the muscle elements to the left of the electrode plotted alone, and the dotted line ending at T_1 represents the electrical effects of accession of activity in the muscle elements to the right of the electrode plotted alone. (The full line in this region is a combination of these effects.)
C is an actual record taken from the central region of a frog's auricle after the preparation had been warmed.

closer, negative. By means of this formula the magnitude of the effect upon the electrode of any potential difference existing in any portion of the muscle can be calculated.

In the center of a long muscular fiber, divided into squares, is a cross (Fig. 9) which serves to indicate the position of the exploring electrode, the tip of which is supposed to be one unit of length above the plane of the paper. *ABCD* represents the familiar arrangement of the process of

activation and recovery. The effect upon the electrode of the electrical events which occur in the first square while its activity is increasing can be ascertained by applying the formula $E = \frac{\mu \cos \theta}{R^2}$.^{*} This effect on the electrode is represented in the figure by the first shaded rectangle below the muscle fiber (the first from the left). Its height corresponds to the electrical effect produced upon the electrode and its length to the duration of this effect. The duration will, of course, be equal to AB , since it is assumed that the velocity with which the process travels is one unit of distance in one unit of time. Once this element has become fully active it will no longer exhibit any potential difference. Thus, for the next seven units of time, no potential difference will exist here. But during the four and one-half units of time while activity is regressing (equal to CD) it again becomes the source of a potential difference, but this time of opposite polarity. This effect is represented by the first long narrow shaded rectangle above the muscle fiber. Since the regression process is three times as long as the period during which activity is increasing, the potential difference produced in a given segment in the first case is one-third that produced in the second. Consequently, this rectangle is one-third as high and three times as long as the one plotted for the period of increasing activity. Furthermore, since the positive pole is always toward the resting muscle, and the negative toward the active muscle in the case of increasing activity, the positive pole will be nearer the electrode and the effect upon it, therefore, positive, and in the case of decreasing activity, the negative pole will be nearer the electrode and the effect upon it negative. Since in electrocardiography the galvanometer is always so arranged that a negative effect produces an upward deflection, the negative effects are plotted above the base line (muscle fiber) and positive effects below.

Next, a similar plot is made of the electrical effects produced in the second square. The rectangles in this case are entirely similar to those for the first segment but both are of greater height, since the segment is closer to the electrode.

In the figure, rectangles have been constructed for each of ten segments, five to the left of the electrode (hatched), and five to the right (hollow). The effects of the segments to the right of the electrode must, obviously be of opposite polarity to those to the left, so that in this case the effects of increasing activity will be plotted above the line, and those of decreasing activity below. All the electrical effects produced are represented in their proper time relations. The first, that of increasing activity, starts when the excitation process reaches the muscle ele-

^{*}In making the actual calculations for this graph and the ones to follow, the width of one square was used as the unit of length and μ given an arbitrary but appropriate value so that the resulting graph would be of a proper size. Negative effects are plotted above the line and positive effects below, to correspond to the conventional method of recording electrograms.

ment and endures so long as this transitional (increasing) state lasts. The second, that of decreasing activity, is plotted not over the muscle element in which it originates, but at the position corresponding to the *time* at which it occurs. Consequently, it is only necessary to take the sum of all the effects present at a given instant to obtain the height of the electrogram at this instant. Thus, any line drawn perpendicularly to the base line (muscle fiber) will cut one or more rectangles. If the segments of the intercepted rectangles are measured and added algebraically, the ordinate of the electrogram for that instant is obtained. Figure 9B is the theoretical electrogram so plotted. It will be seen that the *O* value of the ordinate at T_2 is the result of the sum of two equal but oppositely directed potential differences and not the nonexistence of a potential difference at this time. In the region to the right of T_3 , effects of the regression of activity in segments to the left of the electrode are combined with effects of increasing activity in elements to its right, with the result that the curve does not return to the base line in this region. The dotted lines in the figure represent the effects of the accession and regression of activity in this region of overlapping, plotted independently. It is obvious from the figure that the electrogram is the sum of two diphasic curves, the first the result of the onset of activity, and the second the result of its regression, separated by an interval equal to the period during which each segment of muscle is fully active. It is to the second of these curves that particular attention will be directed, for adequate analyses of the former have already been made.

The recorded curve (Fig. 9C) was obtained from the frog's auricle by the method already described. Its similarity to the theoretical one is obvious. All the essential features of the recorded curve are present in the theoretical one. This particular curve was obtained from the central portion of the auricle after the preparation had been heated by flushing it with warm saline solution. It was chosen for the first analysis because it exemplifies the process in a more general way than do the curves taken under more nearly normal conditions which will be discussed presently. Craib, and Wilson, Macleod, and Barker believed furthermore, from their studies of the primary deflection, that the secondary or T deflection should be of this shape. But if such curves had been obtainable under ordinary circumstances, correct analyses of the secondary deflection undoubtedly would have been made long ago.

In the earlier part of this study the first rapid deflection (QRS) of the electrogram or electrocardiogram has been referred to as the primary, and the slower and later (T), as the secondary deflection. These terms are not satisfactory and were merely used as a convenient means of referring to the parts of the curve. But now that a probable causal relationship has been shown to exist between the first rapid diphasic curve (Fig. 9, $T_1T_2T_4$) and the accession of activity and the second

slower diphasic curve (Fig. 9, $T_2T_3T_4$) and the regression of activity, they will hereafter be designated as the accession deflection and the regression deflection.

It has been assumed that a muscle fiber is long enough to include all stages of activity at one time. But the conditions so far discussed do not represent the normal state of affairs. Obviously, since each small segment of muscle goes through every phase of activity, it is not at all necessary that fibers be long enough to contain at the same time, segments in each and every state from rest to full activity, and back again. It is permissible, therefore, to consider what may happen in a piece of muscle much shorter than the process of activity. In Fig. 10A is represented a short muscle fiber ten units long, the electrode located at the center but removed one segment's length from the plane of the page toward the reader. To the right, the excitation process is schematically represented. In the region AB , activity is increasing, in CB , it is fully developed, and in CD , it is decreasing. CD , the regression process, is more than twice as long as the muscle fiber. It is, of course, understood that length of process means merely the *time* during which activity is decreasing in a single muscle element, times the *velocity* with which the process travels.

If the electrical effects of each element in this short muscle are plotted as in the case of the long muscle fiber previously discussed, a graph similar to that in Fig. 9 is obtained (Fig. 10A). Figure 10B is the theoretical electrogram derived from the graph. The recorded curve (Fig. 10C) with which it is to be compared was obtained from the central region of the frog's auricle at room temperature, that is to say, under ordinary experimental conditions.

It will be noted that the electrogram, as before, is the sum of two diphasic curves, one produced by the electrical effects of increasing activity, and the other by the electrical effects of decreasing activity. Where the effects of decreasing activity (hollow rectangles) overlap those of increasing activity (shaded rectangles), the dotted line represents the effects of decreasing activity plotted alone. In this case it has been assumed that the muscle remains fully active for a short time only, so that the regression process (the effect of decreasing activity) begins very shortly after the accession process. The first phase of the regression process is, in these circumstances, entirely concealed in the larger accession process. This combination of effects necessarily distorts the accession deflection somewhat, rendering it asymmetrical. Since the portion of the regression process which is combined with the accession is an upward deflection, it slightly reduces the depth of the first downward phase of the accession deflection and augments the height of its upward phase. It is noteworthy also that while there is a long isoelectric region separating the first upward and second downward deflections of the regression process, this is the result of a balance between equal

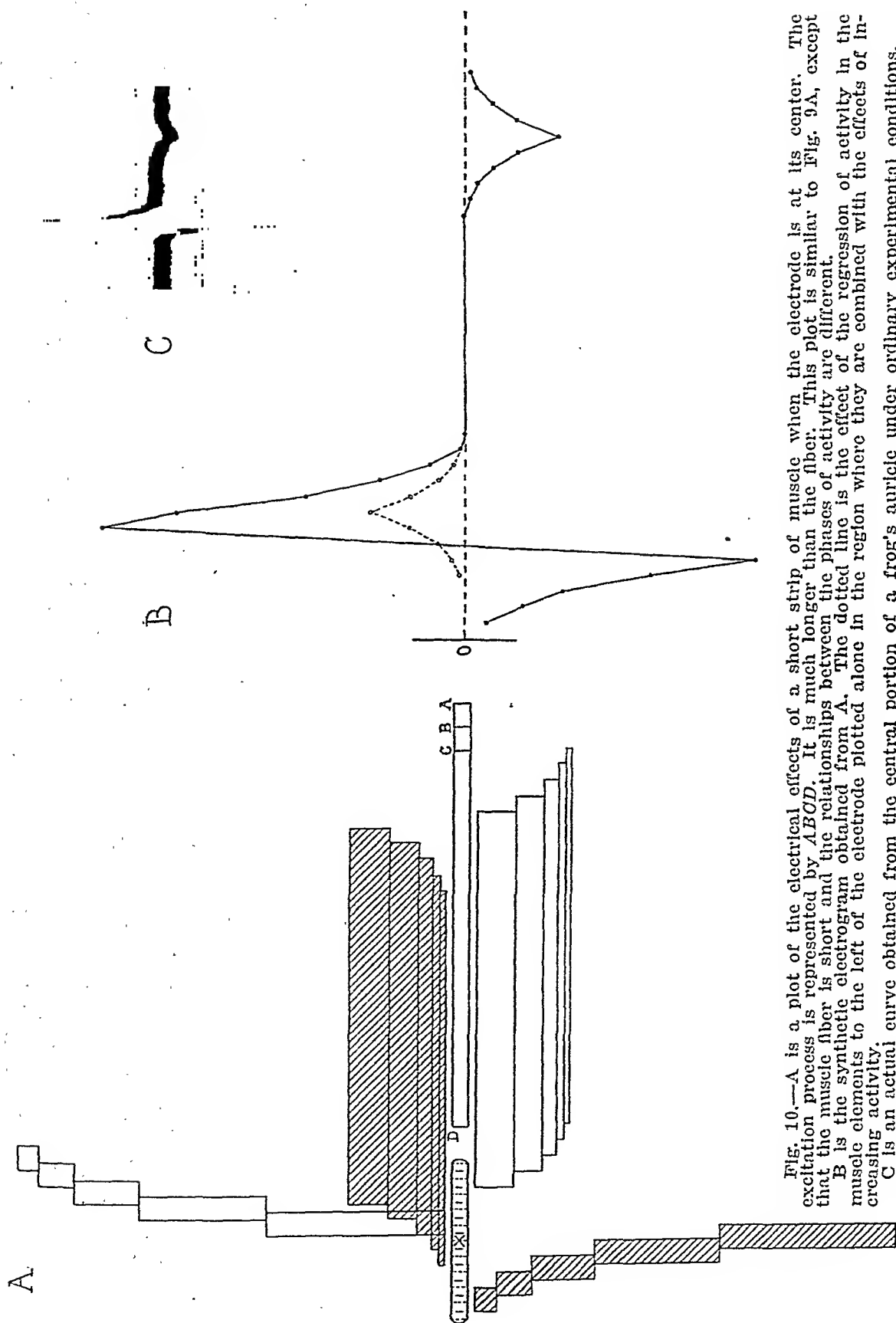


Fig. 10.—A is a plot of the electrical effects of a short strip of muscle when the electrode is at its center. The excitation process is represented by *ABCD*. It is much longer than the fiber. This plot is similar to Fig. 9A, except that the muscle fiber is short and the relationships between the phases of activity are different. B is the synthetic electrogram obtained from A. The dotted line is the effect of the regression of activity in the muscle elements to the left of the electrode plotted alone in the region where they are combined with the effects of increasing activity. C is an actual curve obtained from the central portion of a frog's auricle under ordinary experimental conditions.

and opposite effects in muscle units to either side of the electrode, and does not indicate that no electrical effects are present during this period. This point will be made clearer in the next two experiments.

If, instead of placing the electrode over the center of the muscle strip, it is placed nearer to one end (the end at which the impulse arrives latest) as in Fig. 11A, a distinct change in the type of curve obtained takes place. The graph of the electrical effects produced and the theoretical electrogram are constructed just as in the previous cases. The actual curve with which the theoretical electrogram is to be compared was obtained from the anterior surface of the frog's auricle near the auriculoventricular junction. The similarity between the theoretical and actual curves is again marked. The curve does not return to the base line after the end of the second phase of the accession process, but remains above the isoelectric line for a time and finally dips slightly below it. In this case, the sums of the electrical effects of the regression process in the muscle elements on either side of the electrode are unequal so that the curve does not coincide with the isoelectric line between its upward and downward peaks.

The reverse effect is obtained by placing the electrode near the other end of the muscle strip, that is to say, near the end at which the impulse arrives first (Fig. 12A). The recorded curve which is to be compared with the theoretical electrogram was taken with the exploring electrode near the sino-auricular junction. This record is less satisfactory than the curves illustrating the other cases because its last part is distorted by the occurrence of a ventricular beat, and because in order to expose the sino-auricular junction, the heart was pulled out of its normal position. But the expected features of the curve can be identified and are quite similar to the theoretical electrogram. In this case the portion of the regression process between the two peaks is below the isoelectric line because the equilibrium between the forces on the two sides of the electrode, acting during this interval, has been unbalanced in the direction opposite to that in the previous case.

DISCUSSION

It is apparent from these analyses that the regression deflection is, as Craib and Wilson, Macleod, and Barker believed, a curve of opposite phase to that of the accession deflection. Its first phase may be concealed within the accession deflection and between its upward and downward peaks there may be a portion parallel to the base line. Craib's qualitative reasoning was too indefinite and Wilson, Macleod, and Barker's mathematical analysis too cumbersome to bring out these facts clearly. Discussion of the quantitative relationships between accession and regression processes will be left for a future time but it is obvious that such relationships exist and that an analysis of the T deflection of

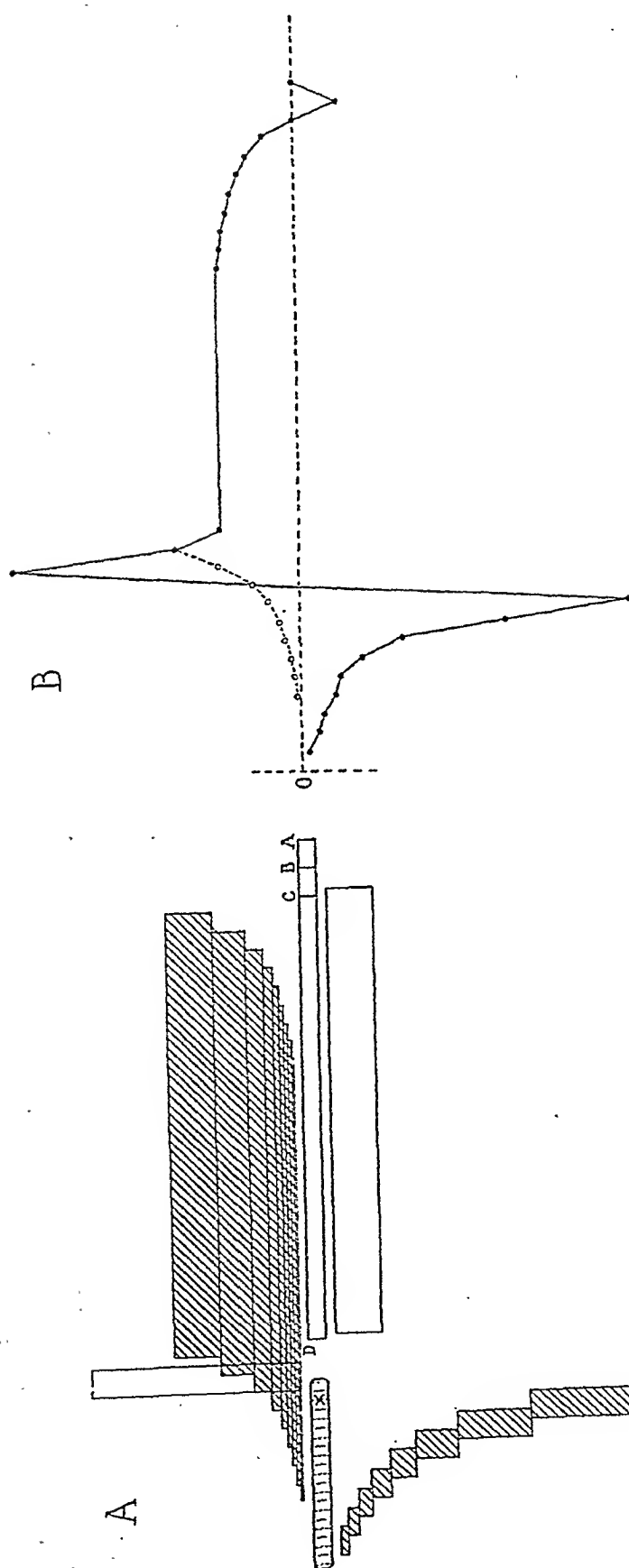


Fig. 11.—A is a plot of the electrical effects in a short strip of muscle when the electrode is near the end which the excitation process reaches last. *ABCD* is the excitation process. It is the same as in 10A. B is the synthetic electrogram derived from A. The dotted line represents the effect of the regression of activity plotted alone. C is an actual electrogram from a point on a frog's auricle near the auriculo-ventricular junction.

the electrocardiogram by means of the areas included by the complexes, such as Wilson, Macleod, and Barker² made, is appropriate.

Since there is evidence to indicate that the form of the electrogram is essentially the same for all forms of cardiac muscle, and since the time relationship between accession and regression processes is similar in electrograms (direct leads) and electrocardiograms (indirect leads), it is probable that part of the regression deflection of the electrocardiogram is really concealed in the accession deflection (QRS) and what has been called the S-T interval, is actually part of the regression deflection. That the S-T segment is an approximately straight line and either coincides with the isoelectric line or is parallel to it depends on the fact that the length of the regression process is longer than the course over which it travels. Coincidence of this portion of the curve (S-T) with the isoelectric line is, of course, fortuitous. If a large number of electrocardiograms is inspected, it will be found, in fact, that the coincidence is seldom exact. According to this view, what has usually been called the T-wave is only the last phase of the regression deflection.

In most discussions of this kind some mention is made of the membrane theory of Bernstein. The theoretical concepts in the early part of this paper are quite different in purpose from those of Bernstein. They do not, as do his, attempt to explain the entire mechanism of stimulation and conduction, but aim only to elucidate one phenomenon, the action current. Whereas Bernstein created an ingenious but imaginary construction which might account for the phenomena observed, the argument here presented consists of logical deductions from facts experimentally ascertained, according to accepted physical methods. Since most of these ideas are quite different therefore from any held by Bernstein when he described his theory, it seems inappropriate to attempt to correlate them with it.*

The assumption has been made that active and resting muscle differ in their constitution and that the contact potential between them gives rise to the action current. The first statement will hardly be denied and the second, since it is an undisputed fact that a potential difference exists between active and resting muscle, becomes self evident if the term contact potential is used in its broadest sense, and no attempt is made to define the possible mechanism by which it is produced. Consequently the argument which has been developed is independent of whatever may be discovered about the significance of minute anatomical structures and the chemistry of activation and recovery. It can shed no direct light on these subjects but may be able to furnish criteria useful in their investigation for it follows from the causal relationship shown to exist between the stages of increasing and decreasing activity and the acces-

It is true that the potential difference between active and resting muscle can be accounted for by the membrane theory when properly interpreted but the method used in the forepart of this paper is more direct and less confusing.

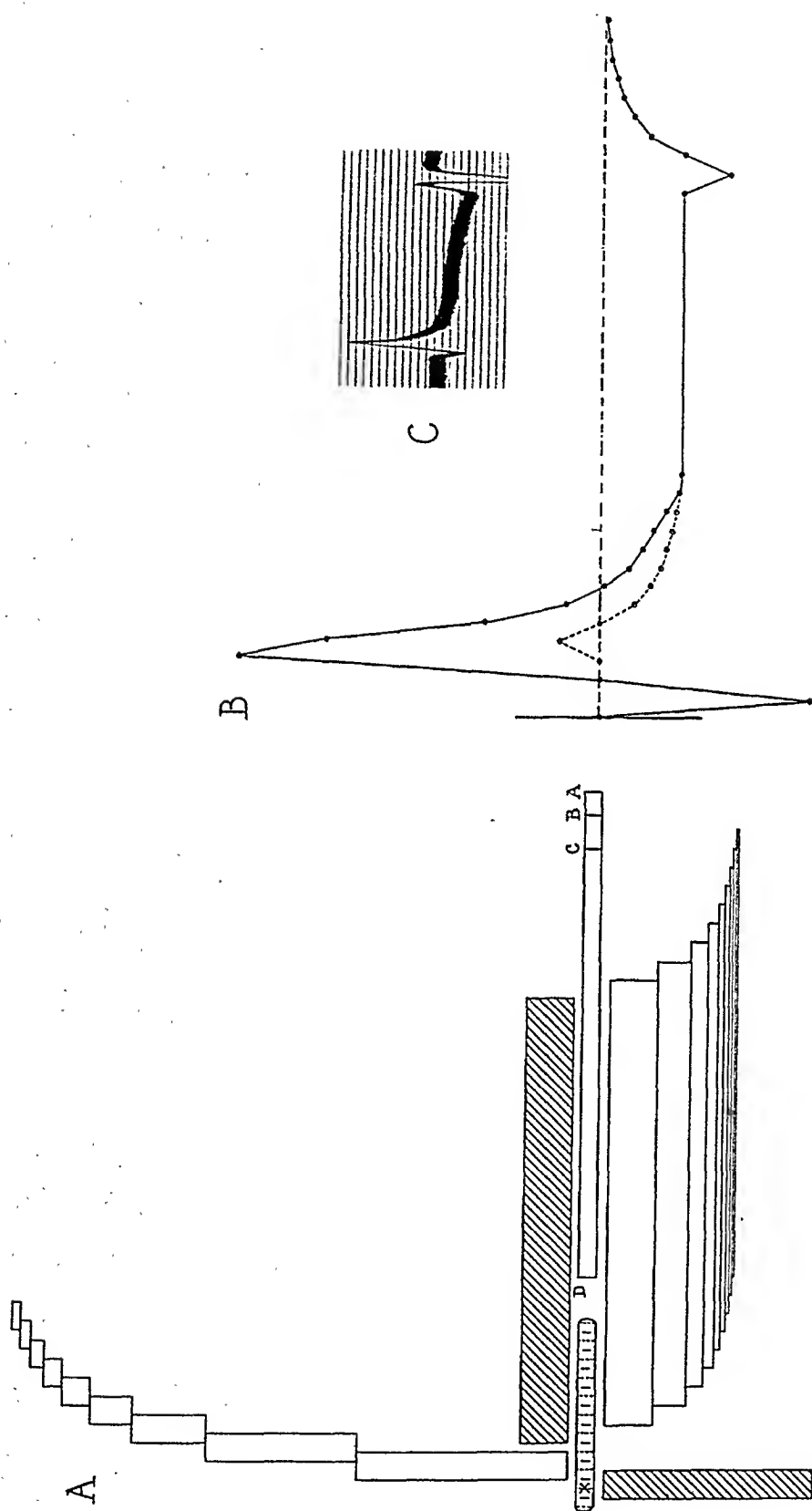


Fig. 12.—A is a plot of the electrical effect in a short strip of muscle when the electrode is near the end which the impulse reaches first. *ABCD* is the excitation process. It is the same as in 10A.
 B is the synthetic electrogram derived from A. The dotted line represents the effect of the regression of activity plotted alone.
 C is an actual electrogram from a point on a frog's auricle near the sino-auricular junction.

sion and regression deflections of the electrogram that it is possible to follow the course of the reactions, as yet unknown, which constitute the processes of activation and recovery.

SUMMARY

1. A method for recording electrograms from the uninjured frog's auricle has been described which approximate those obtainable from a simple strip of muscle.

2. Starting with the observation that a potential difference exists between active and resting muscle, an analysis of the processes of activation and recovery has been made. Based upon this analysis, a graphical method for the construction of a complete theoretical electrogram has been devised. Any assumptions regarding the properties of the excitation process may be made and the appropriate theoretical electrogram plotted. When a theoretical and an actual electrogram accurately correspond, the properties of the excitation process in the muscle which produced the actual curve are presumed to be similar to those assumed in constructing the theoretical one.

3. The regression, like the accession deflection, is expressed in a diphasic curve, the central portion of which may be parallel to the isoelectric line.

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EFFECTS OF INDUCED OXYGEN WANT IN PATIENTS WITH CARDIAC PAIN*

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THE precise mechanism by which painful impulses are initiated in the heart is, as yet, imperfectly understood. There is much evidence to indicate that cardiac pain is due to chemical irritants, presumably acid in character, which are formed during muscular contraction, and that ischemia plays an important causative rôle.¹ Reduction or cessation of blood supply may bring about an increased accumulation of such acid metabolites or may result in failure of the circulation to wash away these substances from the cardiac tissues. Whether the lack of oxygen is itself the stimulus, or whether a pain-producing substance is formed as the result of anoxemia, is not clear.

The present study was undertaken in order to observe the effects of induced, systemic oxygen want in relation to various other factors. Our procedure differed from those previously employed in that (1) a special apparatus was devised by means of which the patient could breathe a constant percentage mixture of oxygen at a rate comparable to that of the normal pulmonary ventilation; (2) the level of anoxemia reached was ascertained by determining the oxygen saturation of the arterial blood; (3) the arm-to-tongue circulation time was measured before and during the test.

TECHNIQUE

Apparatus (Fig. 1).—A tank containing 12 per cent oxygen and 88 per cent nitrogen was used to maintain an unvarying concentration of oxygen in the inspired air. The oxygen mixture was admitted at a rate that was comparable to the normal pulmonary ventilation. The bag was kept full but not distended. By the use of two flutter valves the mixture was inhaled during inspiration and exhaled during expiration, without rebreathing. A two-way valve at the mouth-piece enabled the observer to connect the patient to the apparatus while breathing room air and thus accurately to record the time that he was exposed to inhalation of a low oxygen mixture. A tank containing 100 per cent oxygen was also in the circuit, so that if necessary, by turning a needle valve, anoxemia could be quickly relieved. At the end of each period of observation, the patient was permitted to breathe pure oxygen for several minutes.

Procedure.—Observations were made at least two hours after the last meal. The temperature of the room in which the test was made was kept reasonably constant

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at about 68° F. The patient was allowed to rest in bed for a period varying from twenty minutes to one hour. The procedure was explained and the patient was told that as soon as he experienced pain in the chest or arms, he should raise his hand. A sample of arterial blood taken from the brachial artery was then obtained under oil. The needle for the venous pressure apparatus was next inserted into one of the veins of the arm and a free flow of the column of fluid was assured before proceeding. Through this needle, which was attached to a three-way stop-cock, 5 c.c. of a 20 per cent solution of sodium dehydrocholate was injected and the circulation time, using a bitter taste as the end point, was measured in seconds with a stop watch. The mouthpiece of the gas apparatus was then inserted and the nose clamp adjusted. The patient was allowed to breathe ordinary air through the valve of the apparatus for a few minutes. Control readings of pulse, respira-

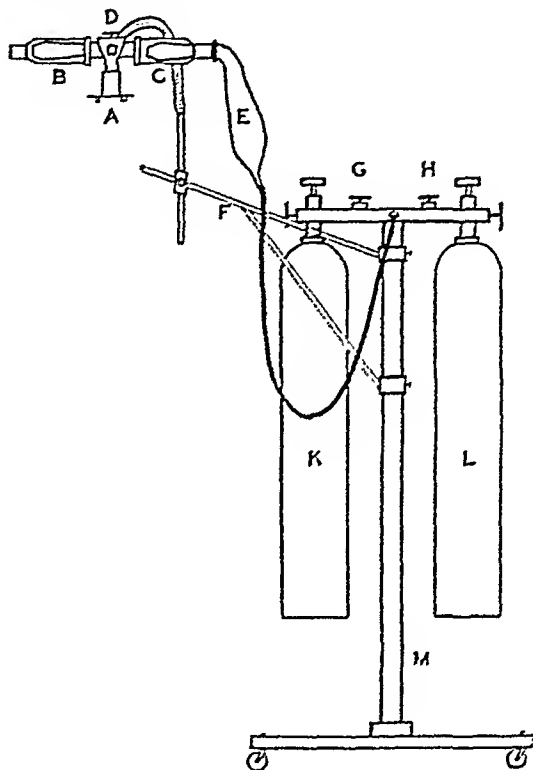


Fig. 1.—Apparatus. A—Mouthpiece. B—Expiratory flutter valve. C—Inspiratory flutter valve. D—Mouthpiece control valve. E—Bag. F—Support stand. G—Nitrogen-oxygen mixture needle valve. H—Oxygen needle valve. K—Tank containing mixture of 88 per cent nitrogen and 12 per cent oxygen. L—Tank containing pure oxygen. M—Tank carrier.

tion, blood pressure, and venous pressure were made until an equilibrium had been reached. The test was then started by turning valve D, as shown in Fig. 1. If pain was experienced the low oxygen mixture was immediately shut off and 100 per cent oxygen was administered. The period of observation was usually no longer than twenty minutes and was never continued longer than twenty-eight minutes. Records of the pulse, respiration, blood pressure, and venous pressure were taken every few minutes. The arterial oxygen saturation and circulation time were determined again only at the conclusion of the experiment.

The above procedure was followed, but without the blood analyses and venous pressure determinations, in those cases in which electrocardiograms were taken. In such experiments, a control record was made and additional curves were taken throughout the period of observation at intervals of several minutes.

MATERIAL

Observations were made on 37 patients with cardiac disease.* Seventy tests were performed; electrocardiograms were taken in ten of these. The clinical diagnoses were: coronary sclerosis with cardiac pain, 30 cases; coronary sclerosis with rheumatic aortic insufficiency, 1; hypertensive heart disease with cardiac pain, 2; aortic stenosis with cardiac pain, 2; syphilitic aortitis and aortic insufficiency, with cardiac pain, 1; rheumatic heart disease with mitral stenosis and insufficiency, 1.

Eleven additional patients without cardiac disease served as controls. The same procedure was applied to them.

RESULTS

Cardiac Pain.—Three of the 37 patients with heart disease did not complain of spontaneous pain; in them, no pain was induced by anoxemia. Of the remaining 34 who gave a history of anginal attacks, only a single observation was made on 23. Of these, 9 had pain during the test; 14 had no discomfort.

In 14 cases, more than one test was done. In 4 patients, no pain occurred. In 7, the result was variable, the patient on some occasions complaining of pain, at other times failing to do so. This variability in response to anoxemia was striking and, it seems to us, important, particularly when compared to the invariable, prompt and sharp response in 2 patients with aortic stenosis. The significance of these results will be considered in the discussion.

In none of the 11 patients without cardiac disease did pain occur.

Heart Rate.—There were 58 observations in 37 cardiac patients. In 34, the rate was accelerated; in 6 there was no change; in 5 the rate was slower at the end of the experiment than at the beginning; in 13 there were slight fluctuations.† There was no correlation between alterations in rate and the occurrence of pain.

Respiratory Rate.—There were 57 observations in 37 cardiac patients. The rate increased in 35; in 3 it was unchanged; in 5 it became slower; in 14 there were slight fluctuations.‡ As was the case with the pulse rate, there was no demonstrable relationship between the respiratory rate and the occurrence of pain.

Blood Pressure.—There were 58 observations in 37 cardiac patients. The systolic level rose in 30; in 4 it was unchanged; in 9, it fell; in 15 there were slight fluctuations.§ The diastolic level rose in 24; in 10 it was unchanged; it fell in 12; in 12 there were slight fluctua-

*We are indebted to Dr. Harold J. Stewart for referring a number of patients from the Cardiac Clinic of the New York Hospital; and to Dr. Arthur C. DeGraff for sending one patient from the Cardiac Clinic of Bellevue Hospital.

†A change of 10 beats or more per minute was considered significant.

‡A change in rate of 4 or more per minute was considered significant.

§A change of 10 mm. Hg or more was considered significant.

tions. Both systolic and diastolic pressures rose more often in the cases that developed pain, and fell more frequently in those that did not. But the association was not invariable. The actual changes observed were relatively small; in only 13 instances did the systolic pressure fluctuate more than 20 mm. Hg; and in only 4 did the diastolic vary to this extent.

*Venous Pressure.**—There was no definite trend in the 18 cardiac patients in whom this was determined. Of the group, 6 experienced pain; and included in this number were the 2 patients with aortic stenosis. In 4 of these 6 patients, a rise in venous pressure occurred, ranging from 12 to 35 mm. of water. Of the 12 cases which did not have pain, 4 showed a higher reading at the end of the experiment

TABLE I

PROTOCOL OF A TYPICAL EXPERIMENT

M. H., male, aged 69. *Diagnosis:* Hypertension; cardiac hypertrophy; sclerosis of coronary arteries; cardiac pain. (Electrocardiogram showed sinus rhythm; left bundle-branch block; prolonged A-V conduction; $T_1 \pm$; T_2 and $T_3 \pm$; $T_4 -$).

TIME	PULSE RATE	RESPIRATORY RATE	BLOOD PRESSURE	VENOUS PRESSURE (MM. H ₂ O)	ARTERIAL O ₂ SATURATION (PER CENT)	CIRCULATION TIME (SECONDS)	REMARKS
10:00							In bed
10:50							Venous pressure needle inserted
11:00					93.6		Sample of arterial blood
11:05	80	24	200/122	81		27	
11:06				80			
11:07							
11:09	80	26	200/118	65			Control
11:10	80	24	200/120	64			Control
11:10½	76			64			Control
11:11							12 per cent O ₂ started
11:11½	80	23	190/124	65		16	
11:12½	84	24	198/126	72			
11:13½				84			
11:14	84	24	218/130	88			
11:15	84	23	200/120	84			
11:16	76	24	194/110	71			
11:18	74	30	168/90	60			
11:19	74	29		50			
11:20			168/98				
11:20½	78	29		53			Pain*
11:21					70.2		Sample of arterial blood
11:22							100 per cent O ₂ given

*Pain described as "the same as when I walk." It was precordial, with radiation to the right arm.

*Venous pressure was measured by the direct method of Moritz, F., and von Tabora, D.: Über eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsch. Arch. f. klin. Med.* 98: 475, 1910.

than in the control readings. The average duration of the experiment was longer in the group without pain—an average of nineteen minutes as compared with eleven for the group with pain.

*Circulation Time.**—This was measured in 18 patients with cardiac disease and in 11 persons with normal hearts (Table II). In some of the cardiac patients the control reading was a little longer than the upper limit of twenty-one seconds observed by others in similar cases without myocardial insufficiency.² This may have been due to the presence of a mild degree of latent left ventricular failure. Except in the two patients with aortic stenosis, the circulation time invariably decreased, that is, the rate of flow became faster. In 5 patients, pain appeared after an average interval of nine minutes, and the average shortening in circulation time was six seconds. In the 10 patients without pain, the average duration of the experiment was twenty minutes and the average shortening was five seconds.

In the two patients with aortic stenosis, the circulation time did not change. This was in sharp contrast to the acceleration observed in the other cardiac cases.

As a general rule, the increased velocity of the circulation was proportional to the increase in heart rate. In about one-third of the cases, however, this relationship did not obtain. In the patients with aortic stenosis, the heart rate increased 26 beats in one instance and fell 12 beats in the other.

In the 11 persons with normal hearts, the changes in circulation time after eighteen to twenty minutes of anoxemia were relatively small, the maximum being a decrease of 4.8 seconds (Table II). Evidently other mechanisms can compensate in large measure for oxygen want, provided there is no cardiac impairment.

Arterial Oxygen Saturation.†—This was determined in 17 persons with cardiac disease and in one normal person (Table II). The control levels ranged from 93.3 to 97 per cent, with four exceptions. In two instances, the control specimens were taken fifteen to eighteen minutes after the conclusion of the experiment, instead of before beginning it (Cases 3 and 23, Table II). The values were 90 and 91 per cent respectively; evidently a proper gaseous equilibrium had not been reestablished. In two other cases the control values were a little low—89.6 and 92.5 per cent respectively. In one of these, emphysema was present; in the other there was profound anemia (Cases 4 and 5, Table II).

*Circulation time was measured according to the method of Winternitz, M., Deutsch, J., and Brill, Z.: Eine klinische brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholinjektion, *Med. Klin.* 27: 986, 1931; *ibid.* 28: 831, 1932.

†Arterial oxygen saturation was determined by the method of Van Slyke, D. D., and Neill, J. M.: Determination of Volumes of Gases in Blood by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* 64: 543, 1924.

TABLE II

EFFECTS OF INHALATION OF 12 PER CENT OXYGEN MIXTURE ON ARTERIAL OXYGEN SATURATION AND CIRCULATION TIME IN 23 PATIENTS WITH CARDIAC DISEASE AND IN 7 PERSONS WITH NORMAL HEARTS

CASE NO.	CLINICAL DIAGNOSIS	AGE	SEX	ARTERIAL OXYGEN SATURATION (PER CENT)		CIRCULATION TIME (SECONDS)		PAIN	DURATION OF EXPERIMENT (MINUTES)	REMARKS
				CONTROL	AT END OF EXPERIMENT	CONTROL	AT END OF EXPERIMENT			
1.	Coronary sclerosis	62	M	97.0	72.2	27.8	20.5	0	20	Had received paravertebral alcohol injections Specimen taken fifteen minutes after conclusion of experiment
2.	Coronary sclerosis	66	M	95.2	84.6	-	-	0	20	
3.	Coronary sclerosis	71	M	90.0*	63.5	21.0	15.0	0	20	
4.	Coronary sclerosis	57	M	89.6	62.6	21.4	-	0	20	Had marked emphysema Had profound anemia Red blood count 2.5 million
5.	Coronary sclerosis	48	M	92.5	50.1	-	-	+	12	
6.	Coronary sclerosis	61	M	96.6	67.8	37.0	34.0	0	18	Went into shock
7.	Coronary sclerosis	60	M	93.6	70.2	27.0	16.0	+	10	
8.	Coronary sclerosis	62	M	95.5	76.2	-	-	0	20	Pressure on chest; experiment stopped
9.	Coronary sclerosis	51	M	-	-	23.2	26.0	0	6	
10.	Coronary sclerosis	51	F	90.0	68.5	11.8	11.2	+	12	
11.	Coronary sclerosis	70	M	95.7	67.6	24.4	17.6	0	20	
12.	Coronary sclerosis	56	M	-	-	28.2	20.0	+	5	
13.	Coronary sclerosis	58	M	96.5	70.0	14.8	13.4	0	20	

In every case, there was marked lowering of the arterial oxygen saturation, the values at the end of the observation period ranging from 50.1 to 82.8 per cent. Excepting the four cases referred to in the preceding paragraph, the lowest level of saturation was 67.6 per cent. In the one patient with a normal heart in whom the arterial oxygen content was determined, the level fell from 96.6 per cent to 67.8 per cent. The degree of cyanosis was, in general, proportional to the degree of unsaturation. But there was no apparent relationship

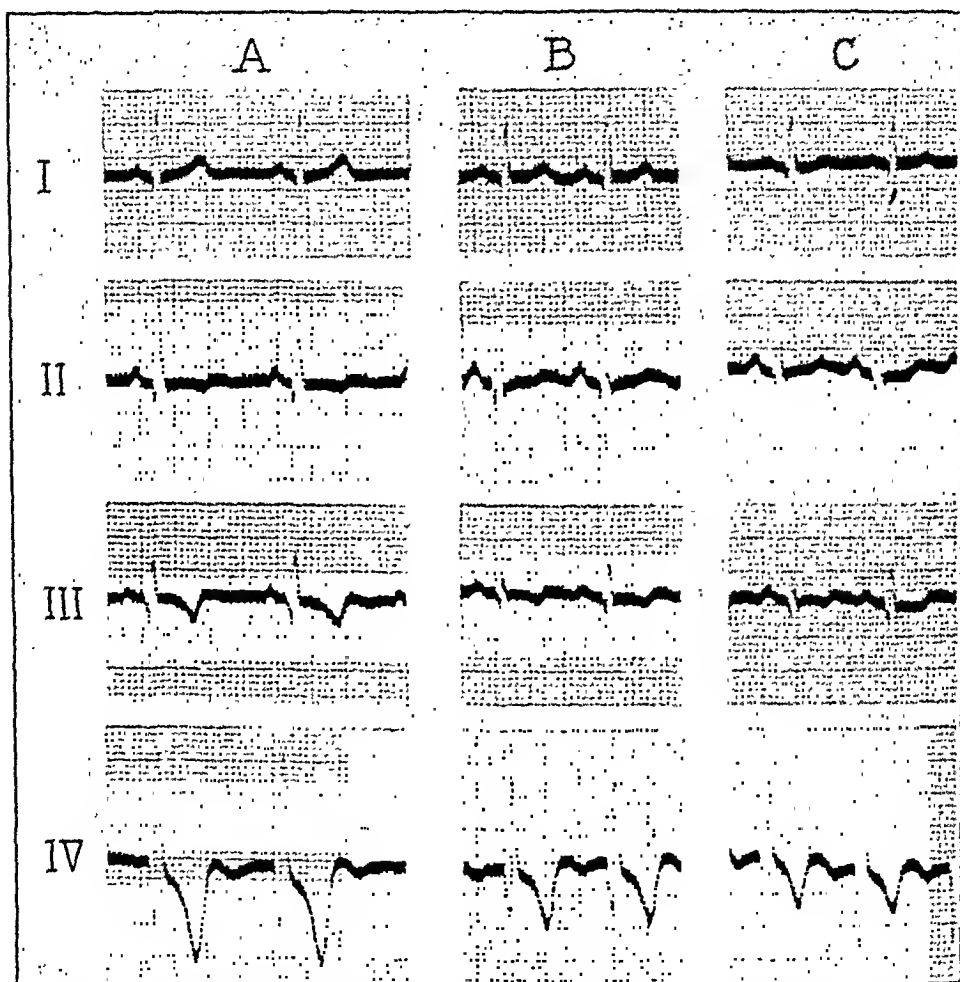


FIG. 2.—Patient with coronary sclerosis and cardiac pain. A—control. B—after inhaling 12 per cent oxygen for one minute. C—after six minutes. Note changes in the contour and amplitude of the T-waves in all leads. The changes in the R-T and S-T segments are slight and are most marked in Lead IV.

between the degree of anoxemia and the appearance or severity of cardiac pain. Nor did the level of oxygen saturation run parallel with increase in heart rate or decrease in circulation time.

Electrocardiograms.—These were taken in 10 patients with cardiac disease. Changes in form were observed in all; in each instance the T-waves altered their amplitude and, occasionally, their direction (Fig. 2). In seven cases, the R-T or S-T segments became depressed in the

three standard leads or elevated in Lead IV (Fig. 3). The heart rate was uniformly accelerated. The auriculoventricular conduction time remained remarkably constant.

In 8 patients without heart disease, changes in the form of the records were also observed in all, but they were of relatively minor degree (Fig. 4). In seven, the T-waves were slightly flattened; in two the R-T or S-T segments were a little depressed. The rate was always increased.

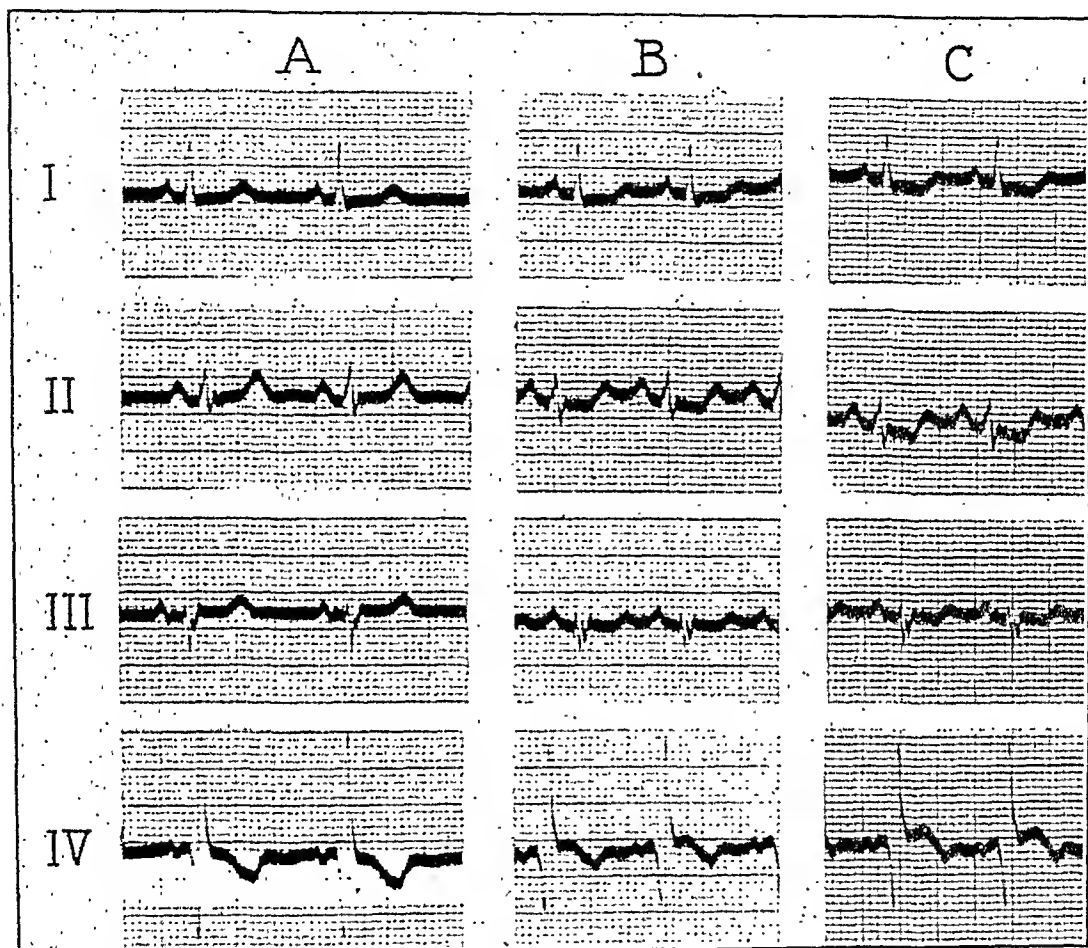


Fig. 3.—Patient with coronary sclerosis who had been given paravertebral injections of alcohol with almost complete relief of cardiac pain. A—control. B—after inhaling 12 per cent oxygen for thirteen minutes. C—after seventeen minutes. Note depression of R-T and S-T segments in the three standard leads, and marked elevation in Lead IV. There are also changes in the amplitude of the T-waves.

Untoward Effects.—In two patients, unpleasant reactions occurred. The first, a man, aged sixty-five years, with coronary sclerosis and cardiac pain, had suffered from an attack of coronary thrombosis seven years previously. The signs indicated that an aneurysm of the left ventricle had developed. Six minutes after beginning the inhalation of 12 per cent oxygen, an attack of typical pulmonary edema appeared. An injection of morphine was given and he was kept in bed in the hospital until the following morning. He was then able to return to his home and experienced no further ill effects.

The second patient was a man, aged sixty-one years, with coronary sclerosis and cardiac pain. He, too, had recovered from an attack of coronary thrombosis three years before. A healed infarct of the myocardium was present, without demonstrable aneurysmal dilatation of the ventricle. Ten minutes after beginning to breathe the low oxygen mixture, the blood pressure began to fall and within another five minutes had dropped from 130/80 to 98/54. The venous pressure fell, coincidentally, from 46 to 6 mm. of water. He presented the picture

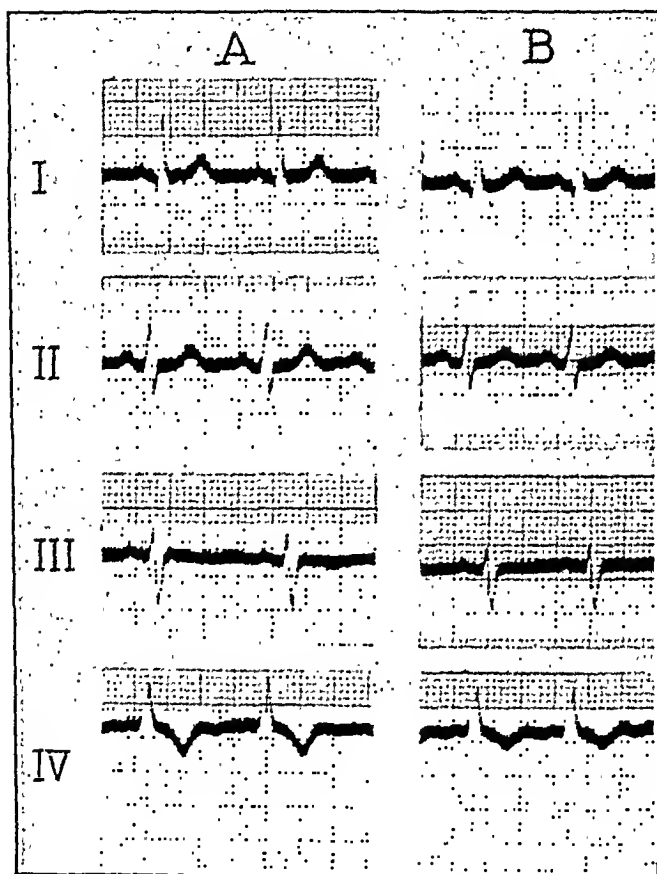


Fig. 4.—Patient with normal heart. A—control. B—after inhaling 12 per cent oxygen for twenty minutes. Note slight flattening of the T-waves in Leads I and II; and less deeply inverted T-wave in Lead IV. There is no effect on the R-T or S-T segments.

of shock. Pure oxygen was administered through the apparatus and ten minutes later the blood pressure had returned to its initial level, although he was still shaky and cold. No cardiac pain was felt by either of these men; presumably the nerve endings in the scarred areas of heart muscle had been destroyed or rendered insensitive to painful stimuli.

A number of patients complained of transient dizziness and dryness of the mouth; but there were no other disturbing incidents.

COMMENT

Other observers, using rebreathing methods, have commented on the inconstancy with which cardiac pain occurs on the induction of generalized anoxemia in patients with spontaneous attacks.³ Rothschild and Kissin noted also the lack of relationship between the oxygen level of the inspired air and the onset of discomfort. They concluded that the response to induced oxygen want was of value in the diagnosis of an impaired coronary circulation. Katz, Hamburger, and Schutz, on the other hand, decided that because of the variability in the results and of the hazard to the patient, "the use of induced anoxemia as a test for the presence of angina pectoris is of questionable value."

Our results, though confirming the variability with which pain occurs, may be interpreted in a manner which will serve to reconcile this difference in point of view. It is understood, of course, that what is said applies only under the conditions of these experiments, namely, a relatively short period of anoxemia and levels of arterial saturation ranging from 67 to 83 per cent. In addition to having shown that pain is not invariably caused by induced oxygen want in different patients with spontaneous attacks, our observations have stressed the inconstancy of its occurrence in the same patient at different times.

The inconstancy in response was not related to changes in heart rate, arterial blood pressure, or venous pressure. There was no critical level of arterial oxygen unsaturation at which pain occurred. But in all cases of cardiac disease studied, with two exceptions, the circulation time decreased—that is, the rate of flow became faster and, presumably, the cardiac output increased.⁴ At times the increased blood supply to the myocardium was sufficient to counteract the effects of the lowered concentration of oxygen. In the two patients with aortic stenosis, repeated tests (6 in one case, 3 in the other) resulted in the prompt and invariable causation of pain. It was in these two cases that oxygen want did not induce a change in the circulation time. That the coronary blood flow is reduced in aortic stenosis has been demonstrated by Green.⁵ Because of mechanical obstruction to the outflow of blood from the left ventricle, acceleration of the rate of flow and coincident increase in cardiac output cannot become operative as compensating mechanisms. Coronary insufficiency, with ischemia of the myocardium, results. In the presence of oxygen want, pain is produced.

Anoxemia, then, must be regarded as an important factor in the causation of cardiac pain. Probably it is not the sole cause.⁶ It is most effective when the coronary flow is reduced; its importance varies directly in proportion to the extent of such reduction. Anoxemia appears to be the determining factor in the process, in the sense that pain occurs only when the supply of oxygen is inadequate. Ischemia

and anoxemia complement each other in synergistic fashion as pain-inducing agents in the heart; neither is wholly effective alone. Thus, extreme anoxemia does not cause cardiac pain in the normal person in whom compensating mechanisms in the circulation are able to function; conversely, the pain following coronary occlusion is often partly or completely relieved by the administration of oxygen.⁷

A number of circumstances are undoubtedly concerned. Of great importance is the emotional status of the patient, as well as his usual ability to appreciate painful sensations.⁸ Other variables are the degree of sensitivity of the afferent nerve endings in the heart, the state of the nervous pathways which conduct pain impulses from the heart to the central nervous system, the total metabolism of the patient and the oxygen-carrying capacity of the blood.

The changes in the form of the electrocardiogram which we have recorded have been previously noted.⁹ They are not specific, for similar alterations can be induced by a number of other conditions. Their description has been included merely to indicate that they occurred under the conditions of these tests. It is well to emphasize that they occurred in patients with normal hearts as well as in those with cardiac disease, but that the degree of change was far greater when the coronary circulation was impaired.

The induction of pulmonary edema and of shock in patients with coronary insufficiency and a damaged myocardium is of practical importance in relation to the effects of oxygen want at the high altitudes encountered in aeroplane flights.⁶ An oxygen concentration of 12 per cent in the inspired air is equivalent, approximately, to an altitude of 15,000 feet. Persons known to have cardiac disease due to an affection of the coronary arteries should not be permitted to ascend to high altitudes.

*Since our paper was written, a remarkable case bearing on this point has been reported by Capt. O. G. Benson, of the Medical Corps, U. S. Army (Coronary Artery Disease: Report of a Fatal Cardiac Attack in a Pilot While Flying, *J. Aviation Med.* 8: 81, 1937). An officer of the Air Corps, aged thirty-four years, had served throughout the war in France. He was a vigorous, healthy man, somewhat overweight. There was nothing in the history to indicate the presence of cardiovascular disease. The blood pressure had always been normal. In November, 1935, while piloting an airplane over the Tehachapi Pass in California, he suddenly experienced a severe pain in the chest. He was the only pilot in the plane, which contained several passengers. Despite agonizing pain, he flew for twenty minutes longer and landed without mishap. He was put to bed at once by a medical officer. Pain continued, cyanosis increased, and he died about an hour later.

At necropsy the heart weighed 441 gm. In the right coronary artery there were several superficial patches of atheroma, but no gross involvement of the smaller branches was seen. The descending branch of the left coronary artery, about 2.5 cm. beyond its point of origin, showed extensive atheroma, involving almost the entire intima to within a short distance of the cardiac apex. The lumen was not much compromised. The circumflex branch was affected in similar fashion. The aorta was practically free from pathologic change. The leaflets of the aortic valve were very slightly thickened. There were several small yellowish patches of atheroma about the base of the aortic leaflet of the mitral valve. No thrombi or emboli were found. There was no infarction of the myocardium. The other organs were normal.

Microscopically, a few of the fibers of the heart muscle were hypertrophied. The medium-sized arteries were sclerosed. There was scarring in the septum, and about one-quarter of the fibers of the main auriculoventricular bundle were destroyed by fibrosis.

Benson remarks that "there is sufficient pathologic change in the heart to justify the conclusion it was the cause of death, precipitated by an attack of angina. Should the pilot's death have occurred in the air with the resultant crash of the plane and death to the other occupants, the conjectures as to the cause of the accident would have been myriad, no doubt. Structural failure of the plane would probably have been the generally accepted explanation."

If such a flight is imperative, provision must be made for supplying the necessary concentration of oxygen.

It is possible that a procedure such as the one described in this paper will prove useful as a test for the functional efficiency of the coronary circulation. It may be expected to detect only those instances in which the coronary reserve is markedly diminished and in which there is failure of compensation under stress. These are the patients in whom acute coronary insufficiency and, on occasion, sudden death are likely to occur.¹⁰ But further studies are necessary to define more precisely the applicability, limitations, and dangers of such a test; at present, it is not recommended for general use.

SUMMARY

1. An apparatus has been described for inducing systemic oxygen want in patients, without rebreathing.

2. Observations were made on 37 patients with cardiac disease and on 11 with normal hearts. A level of oxygen saturation was reached ranging from 67 to 83 per cent, as determined in samples of arterial blood.

3. There was no constant relationship between the occurrence of cardiac pain and changes in heart rate, respiratory rate, blood pressure, venous pressure, circulation time and the degree of arterial unsaturation.

4. Pain occurred inconstantly in repeated tests, except in two patients with aortic stenosis and in one with advanced coronary lesions. In the two patients with aortic stenosis there was no compensatory shortening of the circulation time during the anoxemic period.

5. Untoward effects were observed in two patients with healed infarcts of the heart. Both recovered promptly. The bearing of these experiences on the danger of aeroplane flights for persons with disease of the coronary arteries was discussed.

6. Oxygen want is an important, and apparently the determining factor in the causation of cardiac pain. It is most effective when the coronary blood flow is reduced. Ischemia and anoxemia complement each other as pain-inducing agents in the heart. Other variable circumstances are also concerned.

7. The induction of systemic oxygen want may prove to be useful as a test for coronary insufficiency; it is not recommended for general use at this time.

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THE IMMEDIATE EFFECT OF MERCURIAL DIURETICS ON THE VITAL CAPACITY OF THE LUNGS*

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IT IS the purpose of this paper to present some definite evidence concerning the value of diuretics in improving the respiratory function in patients with heart failure. There have been but few published communications concerning the direct and immediate effects of diuretics on dyspnea, although many authors comment on their value.^{1, 2, 3} It is generally known that the more powerful diuretics like mercupurin and salyrgan are of great help in the presence of congestive failure with peripheral edema, but such improvement in breathing as results from their use might be ascribed to the prolonged rest in bed, digitalis, and other therapeutic measures. It is obvious that the disappearance of edema results directly from the diuretic drug. To appraise the effect of a diuretic on the factor of dyspnea alone it would be preferable to study its effect in cases with no peripheral pitting edema. Harrison⁴ and Friedman, Resnik, Calhoun, and Harrison⁵ have reported a few observations that bear directly on this problem.

A small group of cardiac patients was selected, suffering from breathlessness, in whom there was no evidence of peripheral edema or in whom the edema was only moderate in degree. In most instances the diuretic used was 1 or 2 c.c. of mercupurin given intravenously. In a few cases a similar amount of salyrgan or a mercupurin suppository was given. All the patients were under bed care in the hospital, had been digitalized, and generally were taking ammonium chloride. The specific effect of the diuresis on the respiratory mechanism was judged by measuring the vital capacity of the lungs just before the diuretic was injected and repeating this observation twenty-four hours later. Subjective changes in the degree of dyspnea were also estimated, and changes in the physical findings in the lungs, such as the presence or absence of râles, were noted. The most reliable measure of improvement in breathing has been found to be the vital capacity of the lungs. This objective figure eliminates the error that might otherwise result in estimating a subjective sensation such as respiratory distress.

Table I records the results obtained on 19 observations in nine patients. In all instances there was obvious dyspnea or evidence of pulmonary congestion, or both. In every case, twenty-four hours after the diuretic was given, definite improvement in the respiratory function

*From the medical service of the Peter Bent Brigham Hospital, Boston.

TABLE I—CONT'D

4	50082	68	F	Hypertensive heart disease	12/20/36 1 c.c. mercuripurin 1/5/37 1 c.c. mercuripurin 1/10/37 1 c.c. mercuripurin 1/15/37 1 c.c. mercuripurin	Moderate basal râles with diminished resonance and breath sounds. As after last diuresis. As before. Clear.	Few râles. Less dullness and better quality breath sounds. No râles. Slight dullness at bases.	1380	—	4235	Dyspnea very much less. Dyspnea less. Dyspnea less. No dyspnea.	Vital capacity showed steady improvement though peripheral edema returned between each diuresis.
5	48164	56	M	Hypertensive heart disease	1 c.c. salyrgan	Moderate basal râles. Slight fluid at right base.	Not recorded.	1600	1800	610+	Less dyspnea.	
6	47057	50	F	Rheumatic heart disease	8/4/35 2 c.c. salyrgan 1/18/36 mercuripurin suppository 3/2/36 mercuripurin suppository	Numerous basal râles. Slight fluid right base. Moderate râles, fluid at base. Moderate râles, fluid at bases.	Râles less, fluid gone. Râles much less, fluid gone. Râles much less, fluid gone.	— 1400 —	— 1600 —	2100 3100 4000	Dyspnea better. Dyspnea better. Dyspnea better.	Patient had no cardiac reserve and was in constant failure under ideal bed care.
7	50531	29	F	Rheumatic heart disease	1 c.c. mercuripurin	Few râles at both bases, slight dullness.	Clear.	1625	1900 (48 hr.)	1100+	Dyspnea gone.	Patient had no edema.
8	50219	42	F	Rheumatic heart disease	2 c.c. mercuripurin	Moderate râles at bases, slight basal dullness.	Clear.	1425	1900	2750	Dyspnea gone.	Liver no longer palpable. Patient had no edema.
9	51172	38	M	Hypertensive coronary disease	1 c.c. mercuripurin	Few basal râles. Diminished resonance and breath sounds at right base.	Clear.	2800	3400	6585	Dyspnea gone.	Liver no longer palpable.

took place. This was apparent from the subjective amelioration of the breathlessness and the changes on physical examination of the lungs. The degree of moisture at the bases of the lungs diminished, as evidenced by the absence of râles, the amount of dullness, or the character of the breath sounds. More convincing than the subjective improvement in breathing, which the patients themselves often noticed, was the increase in the vital capacity of the lungs. There were eight patients in whom 12 readings were made before and after a diuresis. The average increase in vital capacity was 290 c.c. The smallest increase was 125 c.c., and the largest was 600 c.c. There were other occasions where a diuretic was given when the vital capacity was not measured, but when improvement in the breathlessness and in the physical findings in the lungs attested to the beneficial effects of the drug. The diuretic effect of the injections was manifested by the prompt and decided increase in the urinary output and the loss of weight which took place during the twenty-four-hour period. The minimum output was 2,150 c.c., the maximum output 6,585 c.c., and the average was 3,319 c.c.

Although this group is small, cases were particularly chosen that did not have massive edema; in fact, most of them had only slight or moderate edema. Of especial importance were those that showed no obvious peripheral pitting. It is in this latter group, which presents the picture of dyspnea without any peripheral edema, that physicians have frequently neglected to use diuretics. We have even seen instances in which the physician resented the suggestion that a diuretic be used because there was no obvious edema. These observations illustrate the beneficial result that may be obtained from diuretics on the distressing symptom of breathlessness entirely apart from the well-known effect on edema.

It may be of some interest to discuss the mechanism by which improvement in respiration may take place following a diuresis. Drinker, Peabody, and Blumgart⁶ showed that the artificial production of pulmonary congestion in cats caused dyspnea and increased the volume of blood in the lungs. This is quite comparable to what occurs in congestive failure. Furthermore, Parker and Weiss⁷ have shown that the capillaries of the lungs in cases of mitral stenosis are markedly dilated so that red blood cells within the center of the stream have little opportunity to absorb oxygen from the alveoli, whereas in the normal lung red cells pass in single rows, being directly exposed to the alveolar epithelium. They also showed that there was considerable pericapillary edema in these cases. Finally, there is adequate evidence to show that the total blood volume is increased in heart failure and that part of this increase is accounted for by passive congestion in the lungs. In this connection it has recently been shown by Evans and Gibson⁸ in edematous dogs that a diuresis is accompanied by a sharp decrease in blood volume. From all this it follows that if a diuretic extracts fluid from the engorged capillary bed of

the lungs, both the amount of the remaining air spaces will increase and the capacity for oxygenation of the blood will improve.

SUMMARY

In a group of nine patients with congestive heart failure in whom breathlessness was an outstanding symptom, the immediate effect of a mercury diuretic on the respiratory mechanism was studied. It was found that the average increase in the vital capacity of the lungs twenty-four hours after the injection was 290 c.c. This was accompanied by a prompt improvement in the subjective symptom of respiratory distress and a decrease in the signs of pulmonary congestion.

It is emphasized that the mercury diuretics have a decidedly beneficial effect in cardiac patients with dyspnea, even in those cases in which there is no peripheral pitting edema.

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ELECTROCARDIOGRAPHIC MANIFESTATIONS AND THE CARDIAC EFFECT OF DRUGS IN VITAMIN B₁ DEFICIENCY IN RATS*

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IN 1930 Drury, Harris, and Maudsley¹ observed a slowing of the heart rate in rats fed on diets deficient in vitamin B₁. This bradycardia was specific for vitamin B₁ and has since been used as a test for the estimation of the vitamin B₁ content in various substances.^{2,3} Pigeons fed on polished rice also show a bradycardia and in some cases heart block.⁴⁻⁷ No definite changes in the electrocardiographic complexes in deficient animals have been noted by Drury, Harris, and Maudsley¹ or by Carter and Drury.⁵ Méhes and Péter⁴ observed slight changes in the electrocardiograms of rice-fed pigeons; i.e., the P-R interval was slightly increased and the S- and T-waves were lower than in normal birds.

In human beriberi patients electrocardiographic changes of varying extent have been reported by a number of observers.⁸⁻¹³ In a discussion of the literature Feil¹⁴ states that in approximately one-third of the cases with "beriberi heart" "low voltage, notching of the QRS in all leads, high T-waves, changing sign of T with recovery, and changes in the P-R interval (variable) were present." In view of the frequent abnormalities, such as T-wave changes, tachycardia and prolonged Q-T interval, recently observed by Weiss and Wilkins^{15, 16} in patients with nutritional deficiency, it was decided to undertake electrocardiographic studies on rats kept on an artificial diet deficient in vitamin B₁, in an attempt to obtain further evidence as to the effects of vitamin B₁ deficiency on the heart and the nature of the changes produced.

METHOD

The following control diet was used:

Modified Osborne and Mendel salt mixture ¹⁷	3.5 per cent
Cornstarch (Duryea)	55.0 per cent
Butter fat	8.5 per cent
Washed casein	18.0 per cent
Dry baker's yeast (Fleischmann's unirradiated)	15.0 per cent
Vitamins A and D were supplied by three drops of cod liver oil daily.	

*This investigation was aided by a grant from the Josiah Macy, Jr. Foundation.
From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Butter was washed with warm water and centrifuged as described by Bliss and Green.¹⁸ At first, commercial casein was shaken for several hours with 60 per cent alcohol, washed thoroughly with more alcohol and the process was repeated on a second day. Later, washed casein* was used after it had been rewashed somewhat less thoroughly with 60 per cent alcohol. Control rats were kept in good condition for many weeks on this diet.

Rats deficient in vitamin B₁ were kept on the same diet, with the exception that the yeast was autoclaved in the presence of base to remove vitamin B₁. Originally, 100 grams of yeast were mixed with enough 0.1 N sodium hydroxide to make a smooth paste (about 125 c.c.) and autoclaved for one hour at a pressure of 20 pounds, in a pan large enough so that the yeast was less than half an inch thick. After autoclaving, an equal amount of 0.1 N hydrochloric acid was added to the yeast, which was then dried under a fan and ground to a fine powder. After using this yeast for eight weeks it was obvious that the diet contained some B₁. Accordingly, the yeast was treated with 1 N sodium hydroxide (pH 8.5 to 9.0) and autoclaved for six hours at a pressure of 15 pounds. Since some of the symptoms produced by this diet suggested that considerable B₂ was also destroyed, rats were later kept on a diet containing yeast which had been treated with 0.1 N sodium hydroxide and autoclaved (15 pounds pressure) for six hours at pH 7.

The body weight, food intake and electrocardiograms were studied on four control and three fasting rats, as well as on 22 rats deficient in vitamin B₁ whose initial weights varied from 70 to 178 grams. In order to ascertain the influence of muscular exercise, four of the vitamin-deficient animals were kept in revolving wheels. All activity could be recorded automatically by a counting device. After about a week the rats learned to run on these wheels and could at times go more than a mile a day.

Rats were allowed to become deficient and then were given subcutaneous injections of aqueous solutions of synthetic crystalline vitamin B₁ (Merck).† In all except a few cases solutions of vitamin B₁ were freshly prepared. Each rat was made deficient and cured several times in this fashion. The doses of vitamin B₁ given were estimated on the basis of the observation¹⁹ that 0.0025 to 0.005 mg. per day is required to promote growth to maximum weight in rats.

Electrocardiograms were taken on the unanesthetized rats at intervals of from one to a few days throughout the study. During the taking of the electrocardiograms the rat was placed on its back on a board to which its feet were tied. Electrodes consisting of several strands of copper wire were dipped in electrode paste and wound about the legs. If the fur was rubbed with a moist cloth, sufficiently low skin resistance could be obtained. The three standard leads were used and in all records the string was standardized. Most of the records were taken on paper running at a speed of 50 mm. per second, but in a few we used a speed of 100 mm. per second.

In order to throw light on the mechanism by which changes due to vitamin B₁ deficiency are brought about, as well as on the sensitivity of the heart in B₁ deficiency, observations were made on the effects of epinephrine, atropine, or strophanthin on normal and on vitamin-deficient animals. Electrocardiograms were taken at frequent intervals for one to two hours after the administration of the drug. In three of the vitamin-deficient animals the effect of section of the vagi was studied.

*Obtained from A. H. Thomas Co.

†We wish to express our thanks to Merck & Co., Inc., Rahway, N. J., for their courtesy in supplying us with crystalline vitamin B₁.

RESULTS

Heart Rate.—Rats, kept on a diet containing yeast which was autoclaved for six hours at pH 8 to 9, began to lose their appetites and failed to gain weight in about 10 days. As is seen in Fig. 1, in a typical case the heart rate fell gradually in four or five weeks from about 500 to 350 or 400 beats per minute. In control rats, after the first few determinations the heart rate remained practically constant from week to week at approximately 500. Vitamin-deficient rats

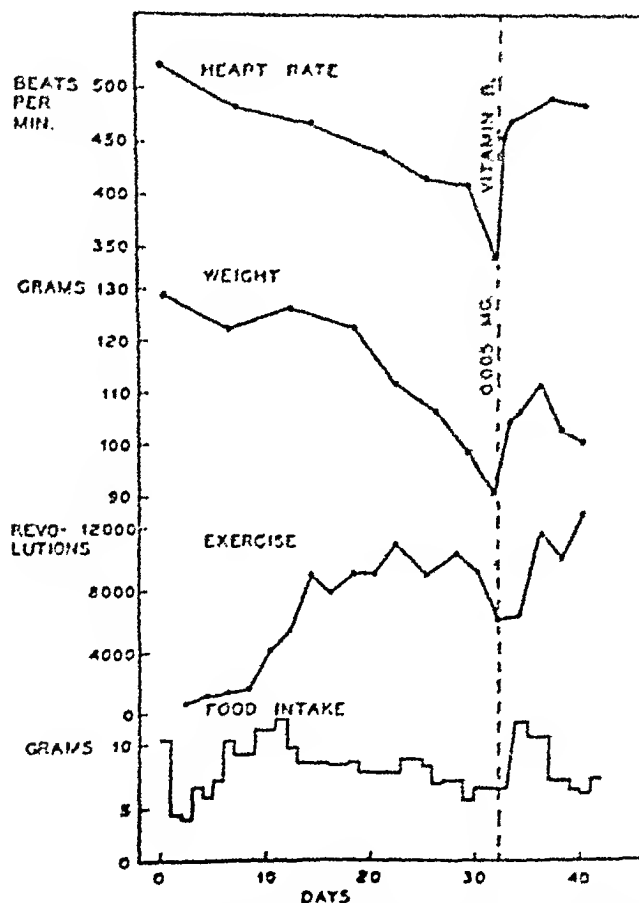


Fig. 1.—Effect of vitamin B₁ deficiency and the injection of crystalline vitamin B₁ on the heart rate, body weight, exercise, and food intake of a rat.

could usually be cured by crystalline B₁ if the rate had not fallen below a level of 350 to 300. When the rats became moribund the rate fell abruptly to from 100 to 200. Drury, Harris, and Maudsley¹ have shown by restricting the food of control animals that the gradual fall in rate to 300 is not due to loss of weight and inanition. We took records on three fasting rats, previously not deficient, in which the rate remained for from three to ten days at about 500 until the day before death, when it fell sharply to from 100 to 200. As previously observed,¹ the rate in vitamin-deficient rats can be raised to practically normal within a few hours with sufficiently large doses of vitamin B₁.

in spite of the fact that food is withheld during this period. Figure 1 shows a case in which the rate rose from 341 to 454 five hours after vitamin B₁, although no food was given. The dose of vitamin administered and the severity of the deficiency determined the number of days before the rate fell again to a dangerous level. Rats can be kept

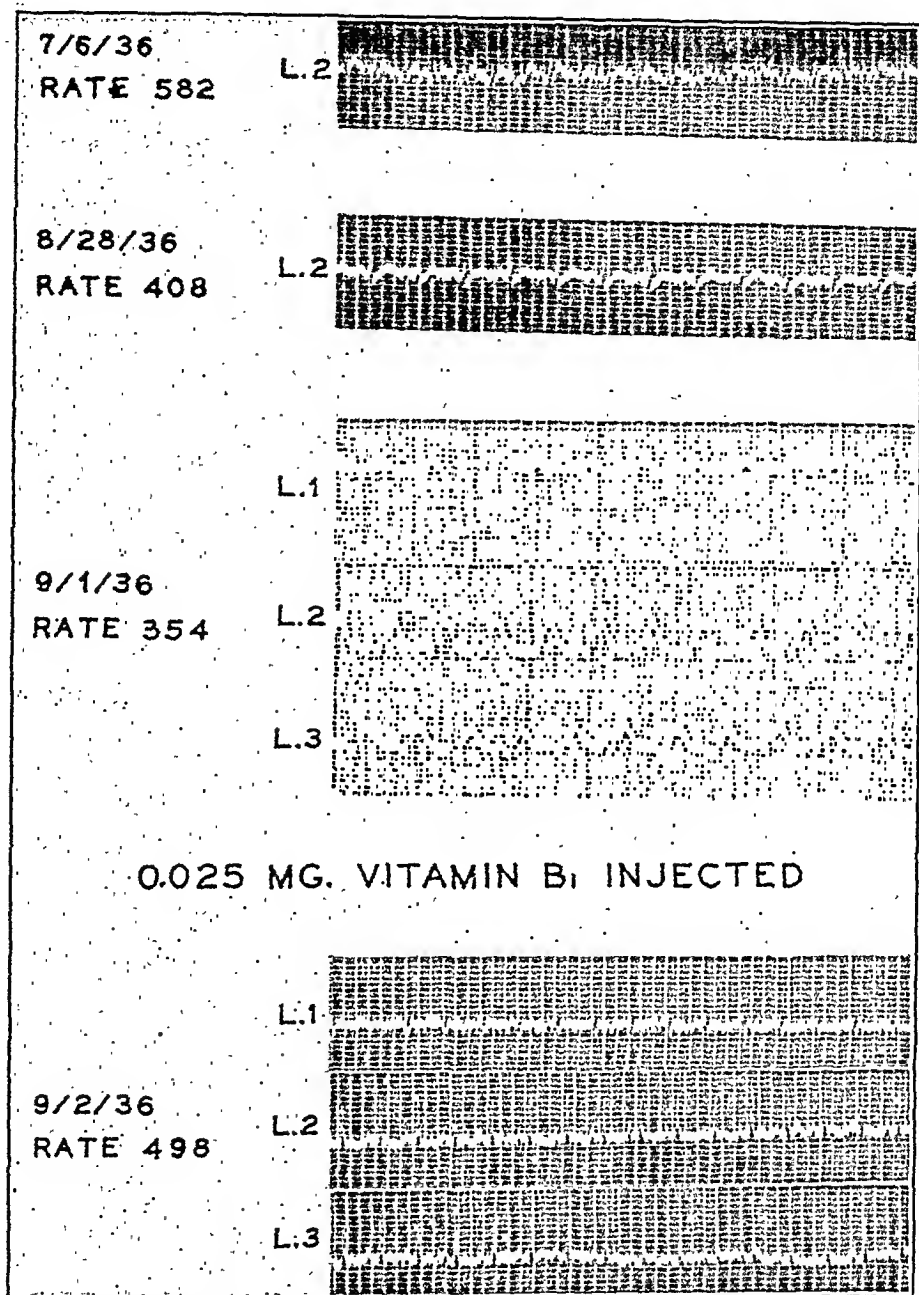


Fig. 2.—Electrocardiograms on a rat fed a diet deficient in vitamin B₁, before and after the injection of crystalline vitamin B₁. The time lines are 1/25 second apart. Note the increase in height of the T-waves on Sept. 1, 1936 and the decrease in height after the administration of vitamin B₁.

in an apparently normal state for long periods on a diet deficient in vitamin B₁ if sufficient crystalline vitamin B₁ is injected.

Electrocardiographic Complexes.—Drury, Harris, and Maudsley¹ did not demonstrate any definite change in the size or the direction of the complexes of their electrocardiograms. Since their records were not

standardized an analysis and comparison of the complexes was not feasible. All but four or five of our series of 22 vitamin-deficient rats showed quite definite changes in the complexes, especially the T-waves, accompanying the decrease in heart rate. In the normal rat electrocardiogram the main deflection as well as the T-waves are upright in

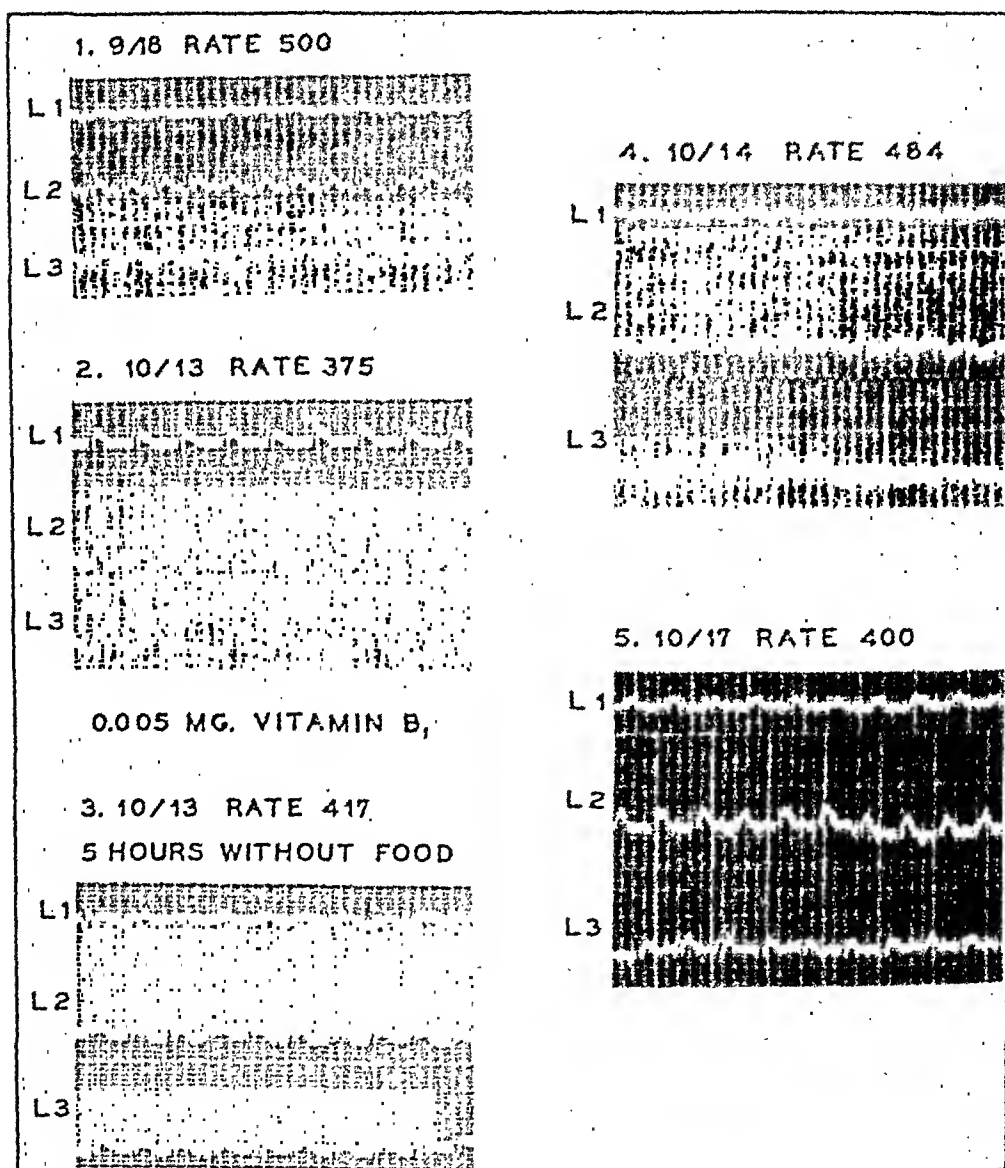


Fig. 2.—Electrocardiograms on a rat fed a diet deficient in vitamin B₁ before and after the injection of crystalline vitamin B₁. The time lines are 1/25 second apart. Note the increased height and the high origin of the T-waves on October 13. Five hours after the administration of vitamin B₁ the T-waves had become lower and within twenty-four hours were inverted.

all leads. Lead I is usually flat, with very small deflections. In our series the main deflection varied between 2 and 8 mm. in normal rats, but as the rats became deficient this gradually increased to from 8 to 16. This did not change to any great extent after vitamin B₁ was injected. The height of T₂ and T₃ normally varied between 0.5 and

2.5 mm. On eight occasions when rats became deficient (with rates between 310 and 410) the T-waves, especially T₂ and T₃, became very high, and on five out of the eight the origin of the T was elevated (Figs. 2, 3, and 4). In the case represented in Fig. 2 the high T-waves disappeared the day after 0.025 mg. of vitamin B₁ was injected, as the

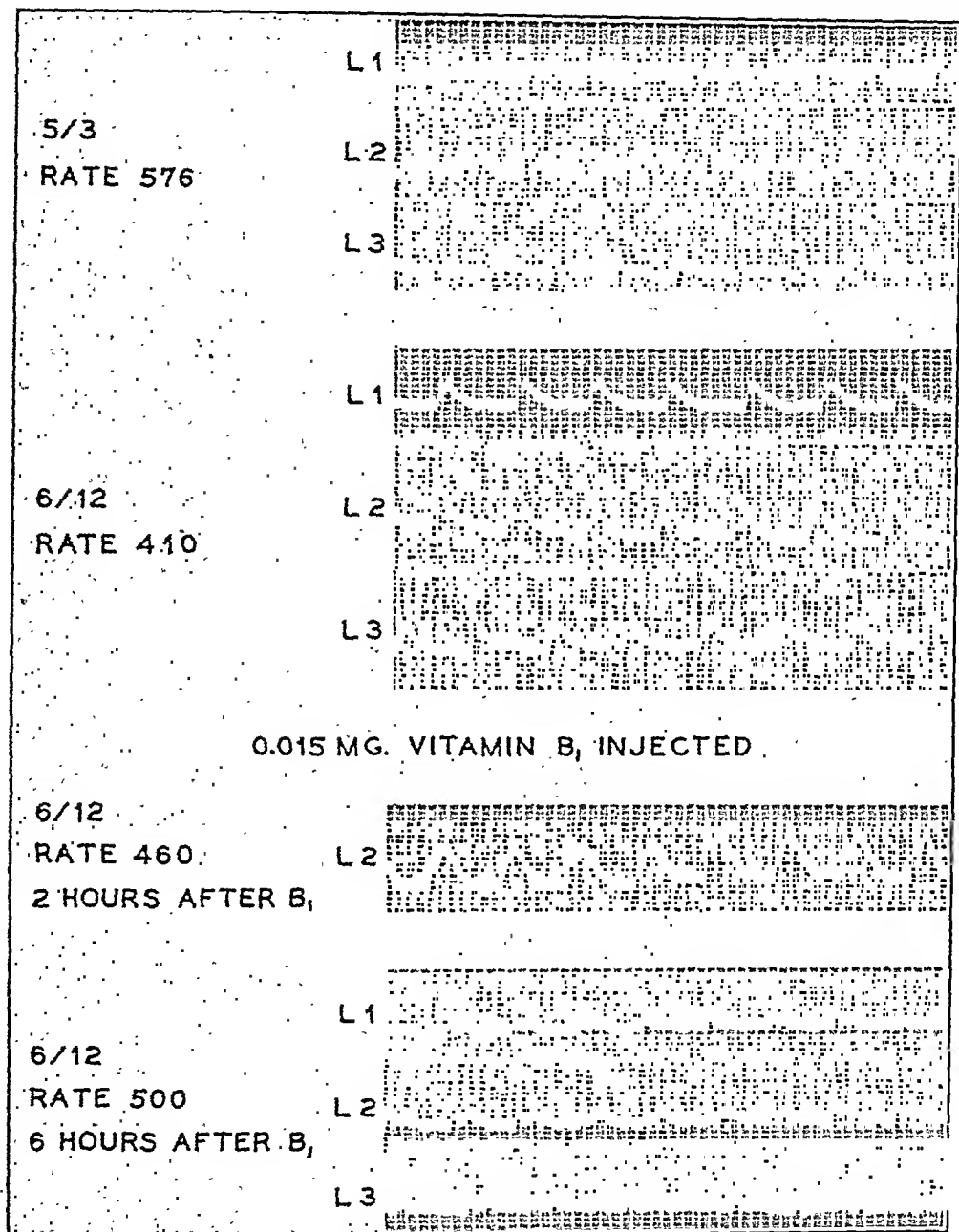


Fig. 4.—Electrocardiograms on a rat fed a diet deficient in vitamin B₁, before and after the injection of crystalline vitamin B₁. The time lines are 1/50 second apart. Note the increased height and the high origin of the T-waves on June 12. Six hours after the administration of vitamin B₁ the T-waves were again practically normal.

rate increased from 354 to 498. In the case shown in Fig. 3, food was withheld for five hours after vitamin B₁ was injected. At this time the T-waves were much lower and the rate had risen from 375 to 417. Food was then given. Eleven hours later the T-waves were inverted and the rate was 484. Three days later the T-waves had again

become upright and normal in size. In another rat, with similar deficiency and a rate of 341, the T-waves became diphasic six hours after vitamin B₁ but without food, and the rate rose to 454. The next day, after food had been given, T-waves remained the same but three days later they were upright and of normal size. Similar temporary disturbances in the T-waves have been observed after the administration of vitamin B₁ and food to vitamin-deficient patients.

In all but two or three instances these high-T-waves were seen the first time the rats became deficient and did not appear subsequently when they were allowed to become deficient with equally low rates.

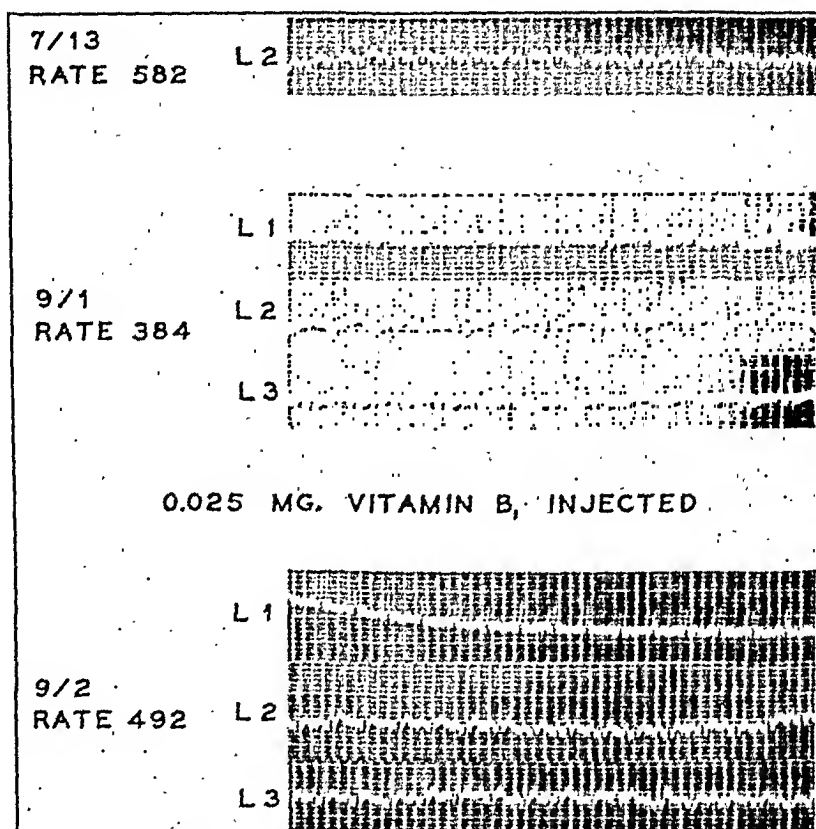


Fig. 5.—Electrocardiograms on a rat fed a diet deficient in vitamin B₁, before and after the injection of crystalline vitamin B₁. The time lines are 1/25 second part. Note the changes in the T-wave on September 1 and its return to normal on September 2.

In many later deficiencies, and in four or more rats the first time they became severely deficient, the T₂ and T₃ became flat or inverted, often with depression of the S-T segment (at rates of from 300 to 430). They usually became upright after vitamin B₁ was given, as is shown in Figs. 5 and 6. The rat represented by Fig. 5 became deficient four successive times with similar changes each time. Occasionally the T became upright while the rate was still low and before vitamin was given, or remained flat when the rate was increased by the injection of vitamin B₁. In the latter instances, however, the doses of vitamin

may not have been large enough to cause prompt changes in the electrocardiogram. In one case T₂ changed from upright to flat with low origin after vitamin B₁ was injected. At certain times rats showed no T-wave changes, although their heart rates fell to the same low levels which had previously accompanied T-wave changes.

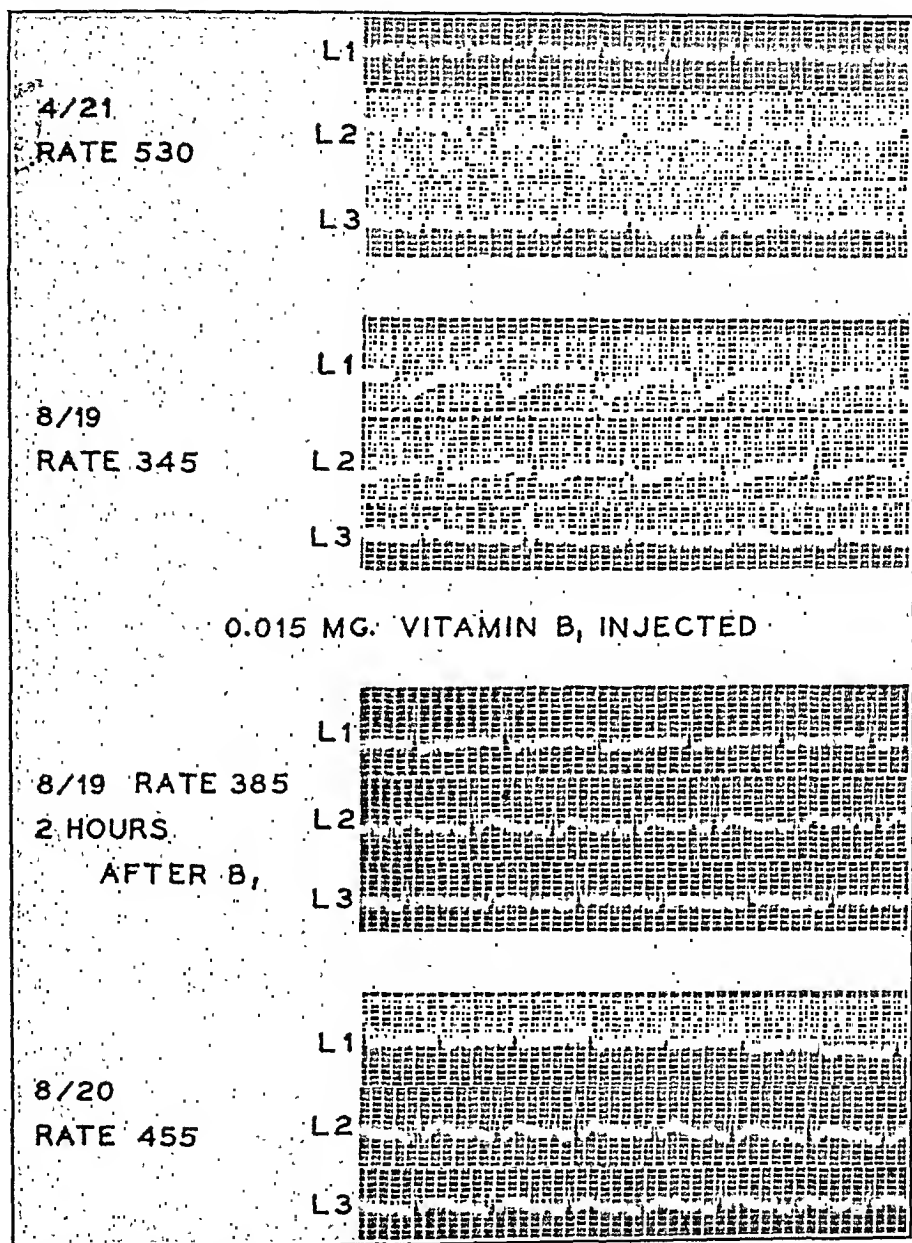


Fig. 6.—Electrocardiograms on a rat fed a diet deficient in vitamin B₁, before and after the injection of crystalline vitamin B₁. The time lines are 1/50 second apart. Note the changes in the T-wave and the depression of the S-T segment on August 19 and the normal complexes after vitamin B₁ was given.

P-R, QRS, and Q-T Intervals.—Our observations confirm those of Drury, Harris, and Maudsley¹ in indicating that although the heart rate falls considerably there is usually no definite change in the P-R or the QRS interval. The speed of the heart rate as well as the presence of somatic tremor often made the records difficult to measure accurately. The P-R interval was lengthened at low rates before death, but in all except four or five cases this set in suddenly and was prob-

ably to be ascribed to the moribund condition of the animal. Previous workers¹ found that the P-wave disappeared at rates somewhat below 350. In only two of our animals did this wave become so low as to be questionable, other rats often showing rates below 350 with definite P-waves. The Q-T interval usually increased as the rats became markedly deficient. The ratio of the Q-T interval to the square root of the R-R interval (K) did not increase as the rate fell and was often somewhat decreased as the rate reached a level of about 400. In fasting rats K increased as the rats became moribund. In many curves the Q-T interval could not be measured in deficient rats because the T-wave did not rise above the isoelectric line.

Exercise.—Only one of the four exercising rats became deficient sooner or showed more marked cardiac changes than the other rats. This may be explained by the fact that they were not forced to exercise and as they became deficient the activity decreased markedly. Cowgill, Rosenberg, and Rogoff²⁰ have shown that dogs which are forced to exercise develop the anorexia characteristic of vitamin lack faster than other dogs. This would be expected since it has been shown that the vitamin B requirement per unit of tissue mass is proportional to the metabolism of the mass. Figure 1 illustrates the decrease in activity before and the increase after giving vitamin B₁ to a deficient rat. In some cases the deficiency was even more marked.

Epinephrine.—Epinephrine hydrochloride (Lederle) in subcutaneous doses of 0.1 and 0.5 c.c. of 1:10,000 solution per 100 grams of body weight did not consistently affect the heart rate in four controls or five vitamin-deficient rats. In two of the three vitamin-deficient rats receiving 0.5 c.c. the T-waves became somewhat higher in from ten to thirty minutes after epinephrine. The third rat had high T-waves before injection and no change was seen. Sixty to ninety minutes after injection several of the vitamin-deficient rats showed irregularities in rhythm not usually seen in the normal rat.

Atropine and Vagus Section.—Atropine and vagus section had little effect on the rate. Atropine sulfate, administered subcutaneously in doses of 2 to 10 mg. per 100 grams of body weight, produced marked symptoms in each of the six controls and five vitamin-deficient rats tested. There was little if any effect on the rate or the complexes in any of the rats. Two vitamin-deficient rats with flat T-waves and one with high T-waves were given 2 mg. of atropine, but no changes in the complexes were observed. Section of the vagi under local anesthesia was carried out on three vitamin-deficient rats. One rat showed a slight increase in rate and another showed longer P-R and Q-T intervals and lower T-waves after vagus section.

Strophanthin.—The action of strophanthin (Merck) was tested somewhat more extensively in order to determine whether the hearts of vitamin-deficient rats were more sensitive to a "digitalis body" than

those of controls. It is known that rats are resistant to the action of digitalis substances. The subcutaneous doses used were 0.5 and 1 mg. per 100 grams of body weight, the fatal dose for a normal rat being about 2 mg. per 100 grams. Of five control rats given 0.5 mg., three showed a definite decrease in heart rate and the other two slight decreases. Of seven vitamin-deficient rats given the same dose, only

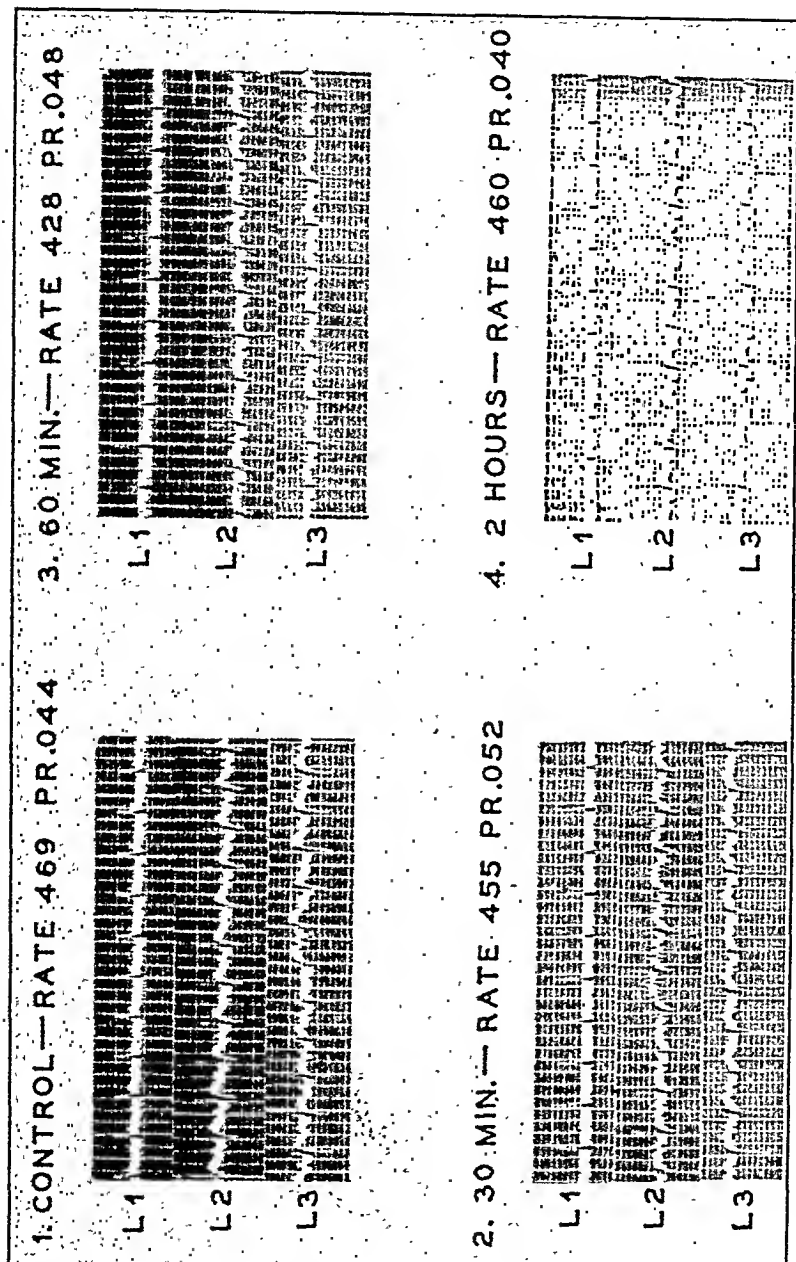


Fig. 7.—Electrocardiograms on a control rat before and after the subcutaneous injection of 0.5 mg. of strophanthin per 100 grams of body weight. The time lines are 1/25 second apart. Note that the electrocardiogram is essentially unchanged after the administration of strophanthin.

two showed some slight fall in rate. The P-R interval was increased in two controls and two vitamin-deficient rats. The difference between the two groups was seen in the changes in the T-waves. Of the controls receiving 0.5 mg. per 100 grams, only one or two had slightly lowered T-waves in Lead II, and three controls given even larger doses (1 mg.) showed no T-wave changes. Figure 7 presents the records of a typical experiment on a control rat in which the T-waves were not definitely altered. Of the vitamin-deficient rats, however,

four showed a depression of the S-T segment or an inversion of the T-wave. In the experiment represented by Fig. 8, T_2 and T_3 were inverted thirty-five minutes after injection of strophanthin, but gradually returned to upright in the next hour and a half. Figure 9 is the record of another vitamin-deficient rat with a slightly lower initial

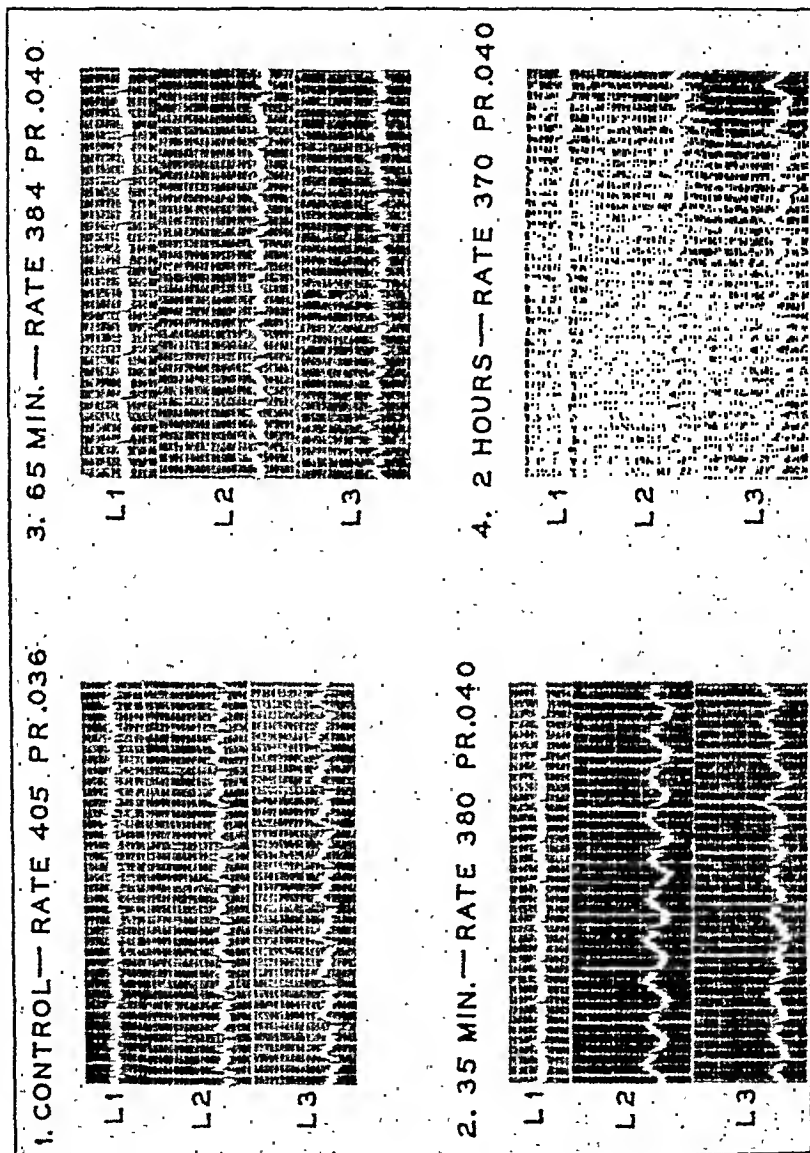


Fig. 8.—Electrocardiograms on a vitamin B₁ deficient rat before and after the subcutaneous injection of 0.5 mg. of strophanthin per 100 grams of body weight. The time lines are 1/25 second apart. Note the change in the S-T segment 35 minutes after strophanthin.

heart rate (390). In this case T_2 and T_3 became inverted, with progressively lower origin, during a period of two hours after the injection. Two of the vitamin-deficient rats died after one-fourth the fatal dose for normal rats. One of these rats showed high T-waves after strophanthin.

This work is in agreement with previous observations,²¹ indicating that the hearts of pigeons fed on polished rice are more sensitive to the effects of strophanthin than those of normal birds. Méhes and

Péter⁴ also found a more marked vagal effect after digitoxin in pigeons with beriberi than in normals.

DISCUSSION

As Drury, Harris, and Maudsley have pointed out, the speed with which the rat's heart recovers after the administration of vitamin B₁

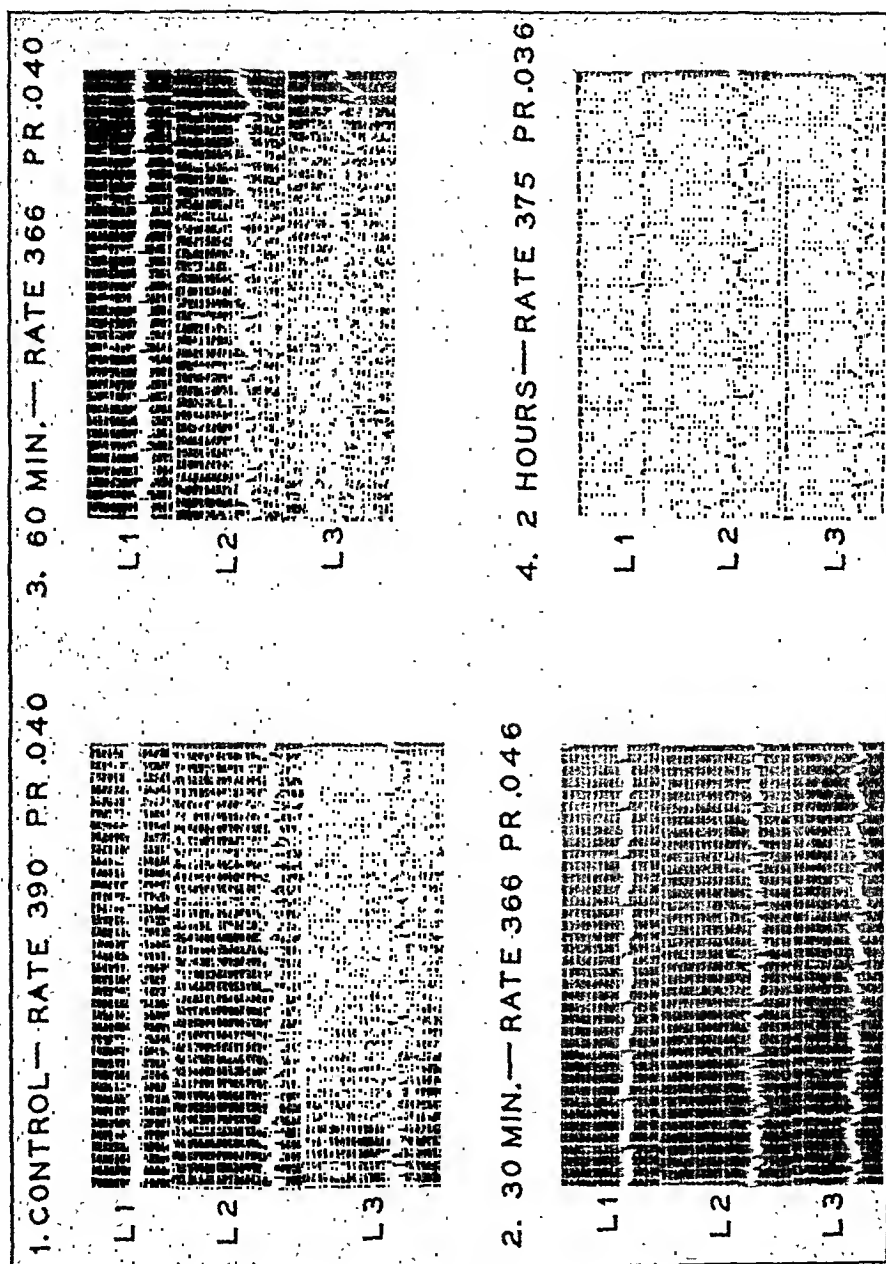


Fig. 9.—Electrocardiograms on a vitamin B₁ deficient rat before and after the subcutaneous injection of 0.5 mg. of strophanthin per 100 grams of body weight. The time lines are 1/25 second apart. Note the progressive changes in the T-waves after strophanthin.

is so great as to rule out an organic degenerative process. If, then, we assume the changes which we have observed to be functional, at least before the deficiency has been very prolonged, they must be explained on the basis of nervous or chemical (hormonal or metabolic) factors, alone or in combination. The bradycardia and heart-block produced in pigeons by feeding them polished rice have been definitely attributed to vagal influence. Carter and Drury⁵ conclude that the heart is probably not hypersensitive but that block is the result of

overaction of the vagal centers. In rats the cardiac effects of vitamin B₁ deficiency are apparently not of vagus origin. In man we have demonstrated that the cardiac changes observed in vitamin B₁ deficiency depend in part on myocardial changes, and in part on changes in the vagus system.^{15, 16} Hypertrophy of the suprarenal gland observed in rats and pigeons with vitamin B₁ deficiency^{22, 23} has been mentioned¹ as bearing on the cardiac effects of the deficiency, but no definite relationship has been found and the issue is confused by the effects of inanition.²⁴

Considerable emphasis has been laid on the metabolic effects of vitamin B₁ deficiency. A number of abnormalities of the carbohydrate metabolism have been reported, including the lowering of the respiratory quotient²⁵ and the increase in the glycogen content of the liver²⁶ in polyneuritic pigeons, the accumulation of lactic acid in the blood of rats² as well as in the muscle, liver, and heart,²⁷ and the accumulation of pyruvic acid in the blood of pigeons and rats.²⁸ Birch and Harris² have pointed out that the defect in lactic acid metabolism is a consistent feature of vitamin B₁ deficiency in various tissues and is present in various species. Inawashiro and Hayasaka²⁹ concluded that lack of vitamin B leads to a disturbance in the re-synthesis of glycogen from lactic acid. The removal of lactic acid is also accelerated by vitamin B. From such evidence Birch and Harris² suggested that the physiological rôle of vitamin B₁ is to intervene, in a capacity corresponding with that of coenzyme, at some stage in carbohydrate metabolism involving the formation and oxidation of lactic acid. They stated that from what is known of the influence of lactic acid on heart rhythm it is to be expected that an excess will diminish the rate of beat in vivo as it does in isolated preparations. Their attempts to influence the rate by the administration of large doses of calcium lactate, however, have been unsuccessful.

More recently Birch and Mapson³⁰ have suggested that the bradycardia in rats and possibly also the disturbed carbohydrate metabolism are due to the accumulation of adenylic acid through failure to convert it into innocuous products.³¹ The relation of lactic, pyruvic, and adenylic acids to the cardiac effects of vitamin B₁ deficiency in rats will be discussed in a subsequent communication.

SUMMARY

1. An analysis has been made of the cardiac rate, electrocardiographic complexes, and the response to drugs of rats in the nondeficient state and in repeatedly induced vitamin B₁ deficiency.

2. The heart rate of rats on a diet deficient in vitamin B₁ fell gradually to a level of from 350 to 300 beats per minute, from which it could

usually be returned to approximately the normal level (450 to 500) within a few hours by adequate doses of crystalline vitamin B₁, even if food was withheld.

3. In all but four or five of the 22 vitamin-deficient rats studied, the decrease in heart rate was accompanied by changes in the electrocardiographic complexes, consisting most frequently of an increase in height, flattening, inversion, or high or low take-off of the T-waves and depression of the S-T segment. With the doses of vitamin B₁ used the T-waves usually returned to normal within from several hours to a day, although occasionally several days were required. The changes in the electrocardiographic complexes had no close relation to the level of the heart rate, and were not identical in the same animals on successive deficiencies.

4. With the exception of very low cardiac rates the P-R interval remained essentially unchanged. The ratio of the Q-T interval to the square root of the R-R interval (K) usually did not increase as the cardiac rate decreased.

5. Only one of four rats which were allowed to exercise on running wheels became deficient sooner than other vitamin-deficient animals. In none of the four exercising rats were the cardiac changes more marked or of different character than those found in the control vitamin-deficient rats.

6. The cardiac responses of normal and vitamin-deficient rats to epinephrine were essentially the same. Occasional irregularities were observed in the vitamin-deficient animals.

7. Atropine and section of the vagus nerves did not abolish the cardiac slowing or the electrocardiographic changes produced by vitamin B₁ deficiency.

8. The vitamin-deficient rats were more sensitive to the toxic effects of subcutaneous doses of strophanthin, and depression of the S-T or inversion of the T-wave supervened with doses which caused no change in normal rats.

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EXTRA SOUNDS OCCURRING IN CARDIAC SYSTOLE*

FRANKLIN D. JOHNSTON, M.D.

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DURING the last five years we have seen a number of patients who have displayed on auscultation a distinct sound occurring in cardiac systole. The character of this sound varied somewhat, but in most instances it was of such short duration that it could best be described as a click. The extra sound frequently gave rise to a gallop rhythm, which, in a few cases, had been confused with the more common type of gallop where the third sound occurs in diastole. Although few reports regarding systolic gallop rhythm are to be found in the literature, Macleod, Wilson, and Barker,¹ Wolferth and Margolies^{2, 3} and White⁴ have briefly discussed the condition and have agreed that its presence has no unfavorable prognostic significance. Gallavardin,⁵ Lian and Deparis⁶ and a few other workers in Europe have reported a number of cases with clicking sounds in systole. On the basis of three autopsied cases where pleuropericardial adhesions were found these observers^{5, 6} believe that the clicks may arise from the presence of delicate strands joining pericardium and pleura. Thompson and Levine⁷ have recently published a clinical study of 35 patients displaying systolic gallop rhythm. They pointed out that the condition is not rare since it occurred in 16 per cent of all patients with gallop rhythm encountered over a period of eleven years. They emphasized further that organic heart disease is usually absent in these patients and that systolic gallop rhythm does not indicate a bad prognosis. It is the purpose of this paper to present a study of 21 cases of systolic gallop rhythm studied by means of sound tracings.

METHODS

In addition to clinical examination of the heart, standard electrocardiograms and x-ray studies of the heart and lungs were made whenever such examinations were possible. All patients were examined by a member of the heart station staff and the diagnosis of systolic gallop rhythm was made or confirmed by auscultation before sound tracings were taken.

Two Einthoven string galvanometers arranged in tandem were employed to record an electrocardiogram, usually standard Lead I, simultaneously with the sound tracing. A condenser microphone arranged in the manner described in a recent communication from this

*From the Department of Internal Medicine, University of Michigan Medical School. This study was assisted by a grant to Dr. Frank N. Wilson from the Horace H. Rackham School of Graduate Studies.

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TABLE I

CASE NO.	AGE	SEX	DIAGNOSIS	CARDIAC SYMPTOMS	PHYSICAL FINDINGS	X-RAY	ELECTROCARDIOGRAM
1	5	M	Cleft lip and palate.	None.	Inconstant systolic gallop at apex. Rough systolic murmur at pulmonary area.	Normal heart and lungs.	Normal.
2	12	M	Rheumatic heart disease with mitral insufficiency.	Pain like pin pricks over heart.	Loud systolic gallop at apex. Faint aortic diastolic murmur.	Normal orthodiagram. Some calcification of hilar nodes.	Normal.
3	15	F	? Rheumatic fever. Neurasthenia.	None.	Tachycardia. Transient extra sound heard best inside apex only in deep inspiration. Blood pressure 118/70.	? active tuberculosis at right apex. Slight hilar calcification.	Normal.
4	17	F	Chronic septic arthritis, left hip.	None.	Systolic click loudest at apex. No cardiac enlargement. Blood pressure 118/68.	-----	P-R interval 0.22.
5	18	F	Psychoneurosis. Hysteria.	Some pain over heart.	Systolic click at apex, disappears on deep inspiration. Blood pressure 118/90.	Small drop type heart. Lungs normal.	-----
6	19	F	Chronic pelvic inflammation (gonococcal).	None.	Click associated with short systolic murmur loudest inside apex. Blood pressure 110/80.	-----	-----
7	19	F	Acute vulgus. Under-nutrition.	None.	Systolic click at apex varying markedly with respiration. Blood pressure 120/70.	Orthodiagram and chest stereogram, negative.	-----
8	20	F	Congenital absence of genital organs.	None.	Lato systolic click and murmur at apex. Blood pressure 138/80.	Prominent conus. Hypoplastic aorta. Slight calcification of hilar nodes.	Flat T's. (digitalis).
9	23	F	No disease.	None.	Click at apex which disappears on deep inspiration and when patient sits up.	Old parenchymal scarring. Slight calcification of peribronchial nodes.	Normal.
10	27	M	Anxiety neurosis.	Palpitation and dyspnea on exertion.	Loud click at apex which disappears on deep inspiration. Blood pressure 145/75.	No cardiac enlargement. Slight peribronchial calcification.	-----
11	28	M	Duodenal ulcer.	Slight dyspnea on exertion.	Highly variable systolic click at apex. Blood pressure 110/60.	Elongation of aorta. Slight tenting of left diaphragm. Slight calcification of hilar nodes.	-----

TABLE I—CONT'D

12	28	F	Hay fever. Asthma.	None.	Fairly loud click at apex. No enlargement of heart or murmurs. Blood pressure 120/75.	-----	-----
13	31	F	Psychoneurosis. Pylorospasm.	None.	Systolic click loudest at apex. No cardiac enlargement. Blood pressure 110/70.	-----	-----
14	31	M	Psychoneurosis.	Pain over heart not suggesting angina pectoris.	Click loudest at apex with patient sitting up, and markedly influenced by respiration. Blood pressure 138/80.	Normal heart and lungs.	Normal except for T's. (digitalis).
15	41	F	Uterine fibroid. ? previous tuberculous infection.	None.	Loud systolic click at apex. Extrasystoles. Blood pressure 120/50.	Borderline sized heart. Slight peribronchial calcification.	Ventricular extrasystoles. Otherwise normal.
16	41	M	Cardiac neurosis.	Pain over heart not like angina pectoris.	Click loudest inside apex. Disappears when patient sits up. Blood pressure 105/84.	Heart not enlarged. Aorta long and tortuous. Moderate calcification of hilar nodes.	Normal.
17	48	F	Hypertensive heart disease. Complete A-V heart block.	Some palpitation and dyspnea on exertion.	Moderate cardiac enlargement. Bradycardia. Apical click heard best on inspiration and much louder with patient sitting up. Blood pressure 160/100.	Tortuous aorta. Lungs normal.	Complete A-V heart-block.
18	51	F	Duodenal ulcer. Renal ptosis bilateral.	None.	Click loudest inside apex. Faint on inspiration but not greatly influenced by change of position. Blood pressure 110/70.	Heart and lungs normal.	Normal.
19	51	F	Menopausa	Slight dyspnea on exertion.	Clicking sounds in systole loudest at apex. Blood pressure 145/90.	Heart not enlarged. Elongation of aorta and calcification of bronchial nodes.	-----
20	67	F	Arteriosclerotic heart disease.	Dyspnea on exertion. Palpitation and slight edema of ankles.	Systolic gallop at apex. Moderate cardiac enlargement. Extrasystoles. Blood pressure 130/70.	-----	Ventricular extrasystoles.
21	71	F	Arteriosclerotic and hypertensive heart disease.	Dyspnea on exertion.	Slight cardiac enlargement. Systolic click loudest inside apex. Extrasystoles. Blood pressure 194/106.	-----	Slight left axis deviation.

laboratory²⁰ was used to take about one-third of the records presented in this series. A crystal vibration pickup²¹ working into a two stage amplifier was employed for the remainder.

Graphic records of the heart sounds furnish objective proof that the extra sounds in question occurred in systole. Further information can be gained by measuring the time intervals separating the peak of the R-wave of the electrocardiogram from the onset of the heart sounds and from the beginning of the extra sound. The measurements given in the article were made with the Lucas comparator. At least four eyeles were measured in each instance.

RESULTS

Table I gives in condensed form certain clinical data pertaining to the patients studied. The cases have been arranged according to the age of the patient, which varied from five to seventy-one years. Half of the subjects were in the second or third decade of life and two-thirds were under thirty-five years of age. Fifteen of the 21 patients, nearly three-quarters, were women. The preponderance of women is probably accidental, since over one-half of the patients studied by Thompson and Levine were males.

A wide variety of clinical diagnoses were made on the patients making up the group. The most frequent diagnosis was psychoneurosis or some form of functional nervous disturbance. This was present in six patients (Cases 3, 5, 10, 13, 14, and 16). Organic heart disease was found in four (Cases 2, 17, 20, and 21), but only the last three had cardiac enlargement or symptoms that indicated myocardial weakness. Arterial hypertension was present in two cases (17 and 21). Lian and Deparis mention that pain over the heart was a frequent complaint of their patients with systolic gallop rhythm, and suggest that pleuro-pericardial adhesions may explain the pain as well as the abnormal sound. Four of our patients complained of precordial pain (Cases 2, 5, 14, and 16) but three of these had psychoneuroses which made the symptom difficult to evaluate.

In all of our patients the systolic click was of maximal intensity at, or a short distance medial to, the cardiac apex, although in many of them it could be heard faintly at the base of the heart. The loudness of the extra sound varied greatly from patient to patient as will be seen by inspection of the curves shown in Fig. 1. Of greater significance was the change in the loudness of the click in a given subject with respiration or shift of position. This variation, usually far greater than coincident changes in the loudness of the heart sounds, was never

²⁰The crystal pickup consists of a slab of especially prepared Rochelle salt crystal supported in a suitable housing so that vibrations from the chest wall are transmitted to the crystal. Voltages proportional to the frequency and magnitude of the mechanical vibrations appear on the faces of the crystal. These small differences of potential, amplified by vacuum tubes, may be recorded by the string galvanometer or other means. The crystal pickup used was designed and built by Mr. G. Howlett Davis.

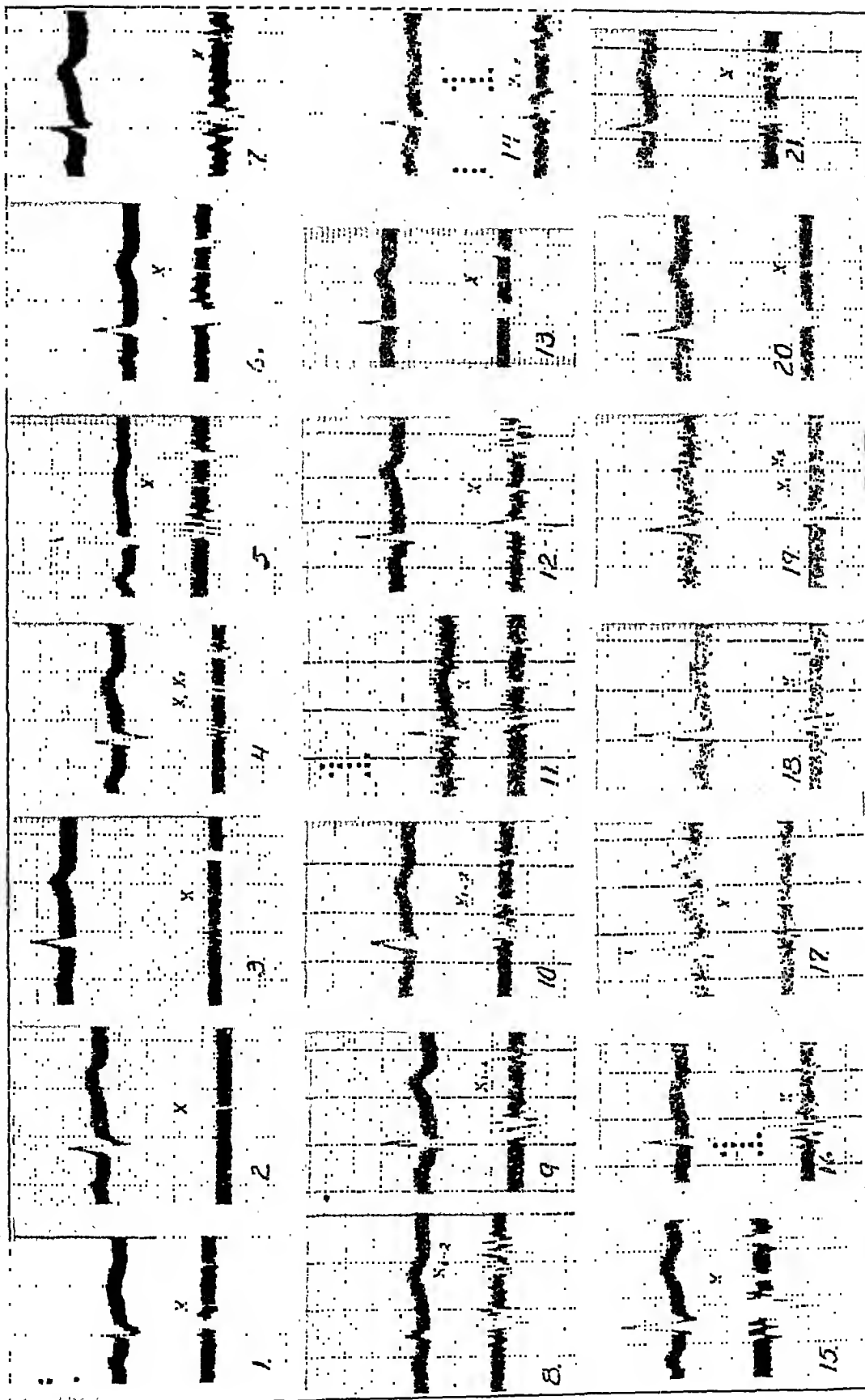


Fig. 1.—The curves corresponding to the cases that were studied (Table I) are arranged consecutively with the case number in the lower left hand corner of each figure. In all figures standard Lead I is the upper curve while the sound tracing taken at or just inside the cardiac apex is the lower curve. The extrasystolic sounds are labeled with an X or when two such sounds were present by X₁ and X₂ or X₁₋₂.

absent when it was specifically looked for. Our clinical notes are incomplete in this respect, but in nine cases a relation between the loudness of the extra sound and respiration or position was noted. In four patients (Cases 5, 9, 10, and 18) the click diminished or disappeared entirely with deep inspiration, while in two others (Cases 3 and 17) the sound was accentuated during inspiration. In two instances (Cases 9 and 16) the extra sound disappeared when the patient sat up, while in two others (Cases 14 and 17) it was loudest with the subject erect.

In addition to the changes in the loudness of the systolic click under different circumstances it was possible occasionally to detect by auscultation that it shifted its position in systole from cycle to cycle. This variation was exhibited to a high degree by Case 1 and is illustrated in Fig. 2A where several heart cycles are reproduced. This subject is discussed more fully in a later section of this article.

It became clear early in the progress of this study that, while the systolic clicks were intimately associated with the motion of the heart, they were probably extracardiac in origin and it was hoped that x-ray studies of the heart and lungs might help to explain their presence. Such examinations were available in fifteen of the cases and the results are included in Table I. Although nine patients had slight to moderate calcification of the peribronchial lymph nodes and one slight tenting of the left diaphragm, no clear-cut evidence of pleuropericardial adhesions was found. Elongation or tortuosity of the aorta or both were found in four subjects. Standard electrocardiograms were taken in thirteen of our cases. Six of these were normal. One showed complete A-V block (Case 17). The remainder showed miscellaneous minor abnormalities, which are listed in the last column of Table I.

Referring to Fig. 1 we see that in five of the patients (Cases 1, 2, 10, 15, and 16) the extra sound was definitely in early systole while in six others (Cases 5-8, 20, and 21) it was late systolic in time. The click occurred nearly in midsystole in nine subjects (Cases 3, 4, 9, 11-14, 17, and 18). In one instance (Case 19) two clicks were constantly present, one in early and the other in late systole. In the majority of the records, from sixteen patients, the extra sound is represented by a series of vibrations lasting not more than 0.03 second. The click in the remaining five patients (Cases 4, 8, 9, 10, and 14) was more or less widely split into two components. In Case 6 the click was followed by a short systolic murmur.

If the clicks under consideration are extracardiac in origin they might be expected to show a greater variation in time with respect to a fixed point of the accompanying electrocardiogram than either the first or second heart sound. Since the exact onset of the first sound is often uncertain, the measurements included in Table II com-

pare the interval between the peak of the R-wave and the beginning of the extra sound with the interval between the peak of the wave and the beginning of the second sound. To demonstrate the relative

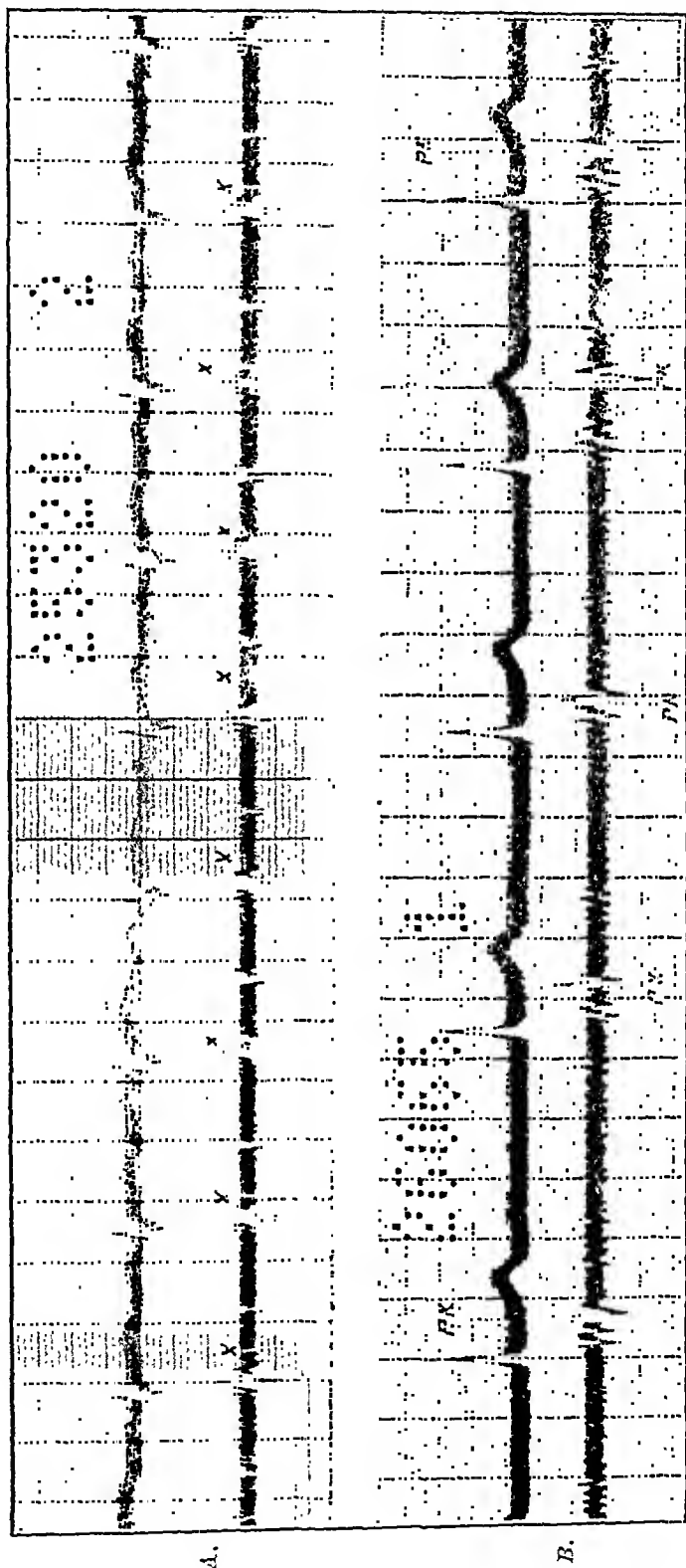


Fig. 2.—The upper curves, Fig. 2A, show eight complexes from Case 1. The position of the extrasystolic sound, labeled X, is highly variable. The lower curves, Fig. 2B, show a "pericardial knock" labeled PK, occurring at different points of systole (see text).

degree of variability between these two sets of measurements the coefficient of variation (defined as the standard deviation divided by the arithmetic mean) has been determined for both sets of measurements. The cases are arranged in Table II according to the magnitude

TABLE II.

CASE NO.	NUMBER OF COMPLEXES MEASURED	AVERAGE TIME FROM		STANDARD DEVIATION		COEFFICIENT OF VARIATION	
		PEAK R TO EXTRA SOUND SECOND	PEAK R TO SECOND SOUND SECOND	R-X	R-SECOND	R-X	R-SECOND
1.	6	0.129	0.283	0.031	0.004	0.242	0.015
2.	4	0.157	0.377	0.025	0.005	0.162	0.012
17.	6	0.215	0.399	0.028	0.017	0.129	0.043
5.	4	0.198	0.320	0.016	0.003	0.081	0.009
11.	4	0.219	0.342	0.017	0.004	0.077	0.011
19.	4	0.176	0.329	0.012	0.007	0.069	0.021
9.	8	0.236	0.352	0.014	0.003	0.058	0.009
6.	10	0.226	0.335	0.011	0.003	0.050	0.009
21.	5	0.264	0.320	0.013	0.001	0.049	0.003
12.	7	0.211	0.380	0.009	0.005	0.045	0.013
16.	6	0.187	0.297	0.008	0.003	0.041	0.011
3.	8	0.181	0.341	0.007	0.004	0.039	0.012
15.	10	0.176	0.335	0.007	0.008	0.038	0.024
20.	5	0.247	0.343	0.009	0.002	0.036	0.005
18.	8	0.206	0.313	0.007	0.004	0.035	0.013
10.	6	0.156	0.343	0.005	0.001	0.033	0.004
13.	8	0.215	0.339	0.006	0.003	0.028	0.009
8.	4	0.245	0.327	0.006	0.001	0.023	0.003
4.	7	0.203	0.353	0.004	0.003	0.020	0.009
14.	5	0.173	0.293	0.003	0.001	0.018	0.003
7.	6	0.304	0.368	0.004	0.002	0.013	0.007

of the coefficient obtained from the measurements which gives the position of the extra sound. It is apparent that the position of the extra sound in the cardiac cycle was much more variable in some cases than in others. The coefficient mentioned varies from 0.242 in the first case (Case 1) to 0.013 in the last (Case 7). This coefficient is, however, uniformly larger than that based on measurements of the second sound. It will be seen that in each case the latter is smaller than the former. It is evident then that in all of the cases the systolic click was more variable with respect to the peak of the R-wave of the electrocardiogram than was the second heart sound.

DISCUSSION

The results presented confirm the opinion formed by other workers that systolic gallop sounds usually occur in patients who show no evidence of organic heart disease and that they have no unfavorable prognostic significance. Although we have no accurate figures on the subject we believe with Thompson and Levine that systolic gallop rhythm is relatively common and that its only clinical importance lies in the fact that it may be confused with diastolic gallop rhythm. One of our patients (Case 14) is a case in point. In this instance the presence of a systolic click had led on a previous occasion to the diagnosis of a serious heart condition and, as a result, the patient had developed a cardiac neurosis which proved very difficult to treat.

The mechanism responsible for the production of extrasystolic sounds is not known. It has been mentioned that Gallavardin and also Lian and Deparis believed the clicks might be due to the presence of pleuropericardial adhesions. Thompson and Levine have referred to two other theories which have been advanced to account for the occurrence of extra systolic sounds. The first, supported by Obrastzow,⁸ Bard,⁹ Giroux¹⁰ and others, presupposes a lengthening of the period of isometric contraction of the ventricle with separation of the elements that usually blend in the normal first heart sound, while the second, proposed by Potain¹¹ and supported by Wiedemann,¹² assumes that distension of an atheromatous aorta can produce the sounds in question. The last of these theories does not adequately explain the occurrence of the clicks in two-thirds of our patients who were under thirty-five years of age and in whom there was no reason to suppose that disease of the aorta could be a significant factor. Furthermore it is not likely that sounds arising in the aorta would be heard with maximal intensity in the region of the cardiac apex or that the loudness of such sounds would be greatly influenced by the position of the patient or by respiration. It is also difficult to understand how systolic clicks can be produced by separation of the elements of the first sound due to abnormal lengthening of the period of isometric contraction. Such lengthening implies an abnormal weakened myocardium, a condition notably absent in the great majority of our patients. Assume, however, for the moment that this difficulty is removed and that the valvular element of the first sound may be delayed enough to be separate from the muscular element. Under these circumstances, an extra sound in early systole, such as was present in five of our patients, might occur but in the remainder of our cases the click was placed primarily in mid or late systole and in these the theory is not tenable.

Margolies and Wolferth have discussed briefly a rare type of systolic gallop rhythm which is heard best at the base of the heart and appears to have the ominous prognostic significance usually associated with diastolic gallop rhythm. None of our cases fit into this group but it is possible that in some of the patients investigated by previous workers, particularly Potain and Wiedemann, the gallop was of this type.

All the evidence both from their clinical characteristics and from the measurements showing the great variability with which the clicks appear in systole indicates that they arise outside of the cavities of the heart and are not dependent upon intraventricular or intra-aortic pressure changes as are the heart sounds and murmurs. It is also apparent that they are in some way produced by the motion of the heart and, since they are so markedly influenced by respiration and the position of the patient, it is difficult to escape the conclusion that the clicks arise from the motion between the pericardium and the

mediastinal or diaphragmatic pleura. We thus return by a somewhat roundabout process of exclusion to the theory that the clicks are due to pleuropericardial adhesions, or to some other anomaly of these structures which allows vibrations to be produced in systole. None of our cases have come to autopsy and the only direct evidence supporting the theory is found in the three autopsied cases of Gallavardin. It is hoped that as time goes on more post-mortem evidence will be available so that the theory can be definitely accepted or rejected. It is possible that roentgen kymographic studies may help to solve this problem.

Before closing this discussion the possible relationship between systolic clicks and the so called "pericardial knock" heard occasionally after spontaneous or traumatic left pneumothorax or during the therapeutic induction of left pneumothorax should be mentioned. These sounds may be loud enough to be heard by an observer across the room from the patient who may be unable to rest because of them. They have been described and explained in different ways by several authors including Rees and Hughes,¹³ Smith,¹⁴ Munden,¹⁵ Hull,¹⁶ Lister,¹⁷ and Wolferth and Wood.¹⁸ These knocks have many features in common with systolic clicks. They are best heard in the region of the cardiac apex, are strikingly influenced by respiration and by position, vary greatly in intensity from time to time, and are sharp short sounds synchronous with the heart beat. Barnwell and Greene¹⁹ have studied a number of patients where the sound occurred during the induction or maintenance of left pneumothorax and believe that the knocks are produced by a highly active heart whose movements are not limited or cushioned by lung tissue either striking the chest wall or the diaphragm held tense by an air containing viscous beneath. It is not certain whether these pericardial knocks always occur in systole but sound tracings with a simultaneous electrocardiogram have been taken from two patients displaying the phenomenon and in both of them the sound occurred in systole. Figure 2B shows one of these records and it will be observed that the knock is represented by vibrations of very large amplitude occurring in different parts of systole.

CONCLUSIONS

Clinical studies on a group of 21 patients displaying systolic gallop rhythm confirm the generally accepted opinion that extra sounds of this type usually occur in the absence of organic heart disease and that their only importance lies in the fact that they are occasionally mistaken for diastolic gallop sounds.

Sound tracings recorded simultaneously with the electrocardiogram were taken on all the patients of the series. Measurements made on these curves indicate that the position of the extra sounds in systole is usually much more variable than is the position of the second sound

with respect to a fixed point of the accompanying electrocardiogram. These results together with the clinical characteristics of the sounds indicate that they are extracardiac in origin. Similarities between systolic clicks and the pericardial knocks heard occasionally in patients with left pneumothorax are pointed out.

The writer wishes to express his appreciation to Dr. Frank N. Wilson for his many suggestions and for his help, particularly in the preparation of this paper.

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A NOTE ON PERICARDIAL INVOLVEMENT IN CORONARY THROMBOSIS*

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THE common conception of the pericardial lesion associated with coronary thrombosis and myocardial infarction is that, when present, it consists of a localized patch of fibrinous exudate overlying the infarcted area. Thus Levine¹ states, "When the process of infarction is sufficient to extend from within the ventricle to its surface, the pericardium is necessarily involved. At this point, a localized fibrinous exudate develops and therefore a true serofibrinous pericarditis will result. It is obvious that if the infarction does not extend to the visceral pericardium, no pericarditis occurs; or if the site of the lesion is in the posterior part of the heart or over the dome of the diaphragm even if the pericardium is involved, a friction rub might not be audible. . . . Only on very rare occasions is pericardial effusion associated with this type of pericarditis."

Similarly Levy² says, "With the formation of an area of infarction involving the epicardial surface, pericarditis develops and a friction rub may be heard. . . . It is heard in a minority of cases. If the infarct is on the posterior aspect of the heart, the rub is not audible. . . . I have never observed effusion in detectable amount associated with the pericarditis of infarction; it has been reported in rare instances. In a few hearts examined at necropsy, adhesions between the two layers of the pericardium in the region of the infarct have been found."

White³ states, "Pericarditis due to infarction is usually limited to the area of necrosis in contradistinction to the general involvement of the pericardium by infection."

On the other hand, Blumer⁴ states that "a usually localized and usually transitory pericarditis is clinically demonstrable in a certain proportion of patients with coronary occlusion, possibly in a third of them. Occasionally much more widespread pericarditis is present, which may involve the entire pericardial sac and eventually lead to its obliteration." The experience in this hospital is in accord with this view.

Sixty cases of coronary thrombosis examined at necropsy form the basis of this report.† In 12 of these the pericardium was normal, while in 48 (80 per cent) pericardial involvement was demonstrated. In the group with pericarditis, the process was localized to the region

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†The authors wish to express their appreciation to the Department of Pathology (Dr. J. W. Jobling, Director) for permission to utilize the autopsy records and in particular to Dr. W. C. von Glahn, for his assistance in reviewing the post-mortem findings in the cases here reported.

of the infarct in 36 (75 per cent) and was generalized so that it involved the whole pericardial surface in 10 (21 per cent). It was generalized, but complicated by, and possibly due to uremia in 2 (4 per cent).

Of the 36 cases of localized pericardial involvement there was a healed fibrous patch or adhesion with an old infarct in 21. Such a lesion would not be expected to cause a rub and none was heard. In 15 cases the infarction was recent and an area of localized, acute fibrinous pericarditis was present. This occurred in the apical region or on the anterior surface of the heart in 12; but in only three of these had a friction rub been heard. The three posterior infarcts on the posterior surface did not produce audible friction rubs.

Excluding the two cases complicated by uremia, the remaining ten with a generalized pericardial reaction fell into two groups. In the first were six cases with recent myocardial infarcts with which there was an acute fibrinous pericarditis; in the second, were four cases with old, healed infarcts and with a more or less firmly adherent pericardium. Three of the recent infarcts involved the anterior surface of the heart, and three the posterior surface. In two of the anterior and in all three of the posterior infarcts a friction rub had been heard during life. Thus the detection of a pericardial friction rub does not rule out the presence of an infarct on the posterior surface since this may cause a generalized pericardial reaction.

Short summaries of the ten cases of generalized pericardial involvement are appended.

SUMMARY

1. In 60 cases of coronary thrombosis with myocardial infarction examined at necropsy pericardial involvement was found in 48 (80 per cent).

2. In the 48 cases of pericardial involvement, the process was localized in 36 (75 per cent), and involved the entire pericardium in 10 (21 per cent). The pericarditis was generalized, but was possibly due to a coexistent uremia, in 2 (4 per cent).

3. A localized acute fibrinous pericarditis was present in 15 cases, but in only three of these had a friction rub been heard during life. A generalized acute fibrinous pericarditis was present in six cases. A friction rub had been heard in five of these, of which three showed the area of infarction to be limited to the posterior surface of the heart.

CASE SUMMARIES

CASE 1.—Unit History 49175. Path. No. 9116. White male, aged seventy-six years. Pain in left chest five days before death. Pericardial friction rub heard. Recent thrombus in left coronary artery. Infarct on posterior surface of left ventricle. "The visceral and parietal pericardium are firmly bound together by a fibrinous exudate which is 0.5 to 1 cm. in thickness in some places, thickest on the wall of the left ventricle."

CASE 2.—U. H. 50293. Path. No. 9130. Obese white female of sixty-four years. Pain twenty-three days before death. Friction rub heard. Circumflex branch of left coronary artery occluded. Infarct on posterior surface. "The epicardium is everywhere covered with a fibrinous exudate."

CASE 3.—U. H. 56243. Path. No. 9448. White male, aged fifty-two years. Attacks of precordial pain forty days and again three days before death. Friction rub heard. Recent thrombus in anterior descending branch of left coronary artery. Apical infarct. "The pericardium is everywhere bound to the heart with recent white fibrinous exudate."

CASE 4.—U. H. 58781. Path. No. 9456. White man of fifty-five years. Pain for a few days. Friction rub heard. Recent thrombus in anterior descending branch of left coronary artery. Apical infarct. "The anterior and lateral surfaces of the sac are everywhere bound to the heart by recent fibrinous exudate which is easily torn off."

CASE 5.—U. H. 244488. Path. No. 10397. White woman of fifty-four years. Pain for three days before death. Friction rub heard. Recent thrombus in right coronary artery. Infarct on posterior surface. "The entire surface of the heart, particularly the ventricles and the posterior portions, are covered with loosely adherent fibrin strands."

CASE 6.—U. H. 420724. Path. No. 11801. White male, aged fifty years. Attacks of pain ten months, five months, and one week before death. No friction rub. Old thrombus in anterior descending branch of left coronary artery; recent thrombus in right coronary artery. Infarcts on anterior surface and at apex. "Over the entire right auricle, a portion of the lateral and posterior walls of the right ventricle, and the posterior surface of the left ventricle there is a thin, shaggy, friable, light yellow exudate."

CASE 7.—U. H. 63053. Path. No. 9657. White male of seventy-four years. Pain followed by progressive congestive failure for eleven weeks before death. Anterior descending branch of left coronary artery occluded. Apical infarct. "The heart is covered by firmly adherent pericardium with complete obliteration of the sac."

CASE 8.—U. H. 63637. Path. No. 9663. White male, aged sixty-eight. No history of pain. Congestive failure for 2 days before death. Old occlusion of anterior descending branch of left coronary artery. Anterior surface infarct. "The pericardial cavity is completely obliterated by loose fibrous adhesions. . . . Where the pericardium had been separated, the epicardium is covered with fibrous tags."

CASE 9.—U. H. 63744. Path. No. 9673. White man of sixty years. No history of pain. Old thrombus in anterior descending branch of left coronary artery. Anterior surface infarct. "The pericardium is found thickened throughout and adherent to the heart."

CASE 10.—U. H. 56480. Path. No. 9828. White man of forty-two years. Angina pectoris for three years. Severe pain and friction rub a year before death. Old occlusion of anterior descending branch of left coronary artery. Anterior surface infarct. "The parietal pericardium is everywhere bound to the heart by dense adhesions."

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Special Article

STANDARDIZATION OF PRECORDIAL LEADS

SUPPLEMENTARY REPORT

THE American Heart Association and the Cardiac Society of Great Britain and Ireland have recently published¹ joint recommendations bearing upon the standardization of a single precordial lead for routine use. Many workers employ multiple precordial leads and the use of such leads is rapidly increasing. The Committee on Precordial Leads of the American Heart Association feel, therefore, that it is desirable to make recommendations with reference to leads of this type. They wish also to make public the considerations which led to the recommendations adopted.

MULTIPLE PRECORDIAL LEADS

When leads from two or more precordial points are employed, it is suggested that the precordial electrode be paired either with an electrode on the left leg or with a central terminal connected through equal resistances of 5000 or more ohms to electrodes on the right arm, left arm, and left leg. It is suggested further that in the first case the letters CF* followed by a subscript and in the second case the letter V followed by a subscript be employed to designate such leads.

The position of the precordial electrode shall be indicated by the subscript used according to the following plan: Subscript 1 shall be used for the right margin of the sternum; 2, for the left margin of the sternum; 3, for a line midway between the left margin of the sternum and the left midclavicular line; 4, for the left midclavicular line; 5, for the left anterior axillary line; and 6, for the left midaxillary line. When the letters and subscripts specified are employed, it shall be understood that in the case of the sternal leads the precordial electrode has been placed in the 4th intercostal space and that in the case of the other leads it has been placed upon a line drawn from the left sternal margin in the 4th intercostal space to the outer border of the apex beat (or to a point at the junction of the midclavicular line and

*Those who prefer to place the distant electrode on the right arm may indicate its position by using the letters CR followed by a subscript. When this electrode is placed on the left arm, the letters CL followed by a subscript may be used. The letters R, L, and F are used as abbreviations for right arm, left arm, and foot (left leg), respectively. The letter C is an abbreviation for chest; T, for central terminal, and V, for voltage. The last (V) is used only in connection with unipolar leads in which the central terminal is the indifferent point.

the 5th intercostal space) and continued around the left side of the chest at the level of the apex beat or of the junction mentioned.†

EXPLANATORY REMARKS

Size of the Precordial Electrode.—There are at present no data upon which an accurate estimate of the most desirable size for the precordial electrode can be based. Theoretical considerations suggested that until such data become available it is desirable to employ a precordial electrode no larger than is required to avoid certain technical difficulties that may arise when a very small electrode is used. The technical difficulties in question depend upon polarization of the small electrode and high skin resistance when a string galvanometer is employed, and involve drifting of the baseline and interference due to extrinsic alternating current when the amplifier type of electrocardiograph is used. A circular electrode 3 cm. in diameter has been found satisfactory.

Single Precordial Leads.—The evidence at present available indicates that when a single precordial lead is used, the best place for the precordial electrode is at the outer border of the cardiac apex. An apical lead appears to give reliable evidence of infarction of the anterior wall of the heart and of abnormalities of the processes upon which the T-wave depends more often than any other single lead from the precordium. The normal variations of the precordial electrocardiogram in apical leads have been more thoroughly investigated than the normal variations of the precordial electrocardiogram obtained by leading from other points. The use of an apical lead has been objected to on the ground that it may be difficult for technical assistants to locate the cardiac apex. This objection applies more or less to all precordial leads. It is, perhaps, less valid in the case of sternal leads than others, but a single sternal lead is not satisfactory for the detection of infarction of the anterior or left lateral wall of the left ventricle.

Because the position of the second electrode is not always a matter of complete indifference, it was decided that it would be best to regard as permissible any of the positions of this electrode which have been specified and to devise a method of designating the one used. It was the general opinion that the committee should recommend one of the locations mentioned as the standard for routine use, but there was an almost even division of opinion as to whether the preference should be given to the right arm, for the sake of convenience in making the

†It will be noted that lead CF₄ and Lead IV F (or lead CR₄ and Lead IV R) may sometimes be identical. In the case of the latter (Lead IV F or Lead IV R), however, the precordial electrode is placed at the outer border of the cardiac apex regardless of the position of the apex with reference to the bony landmarks of the chest, whereas in the case of the former (lead CF₄ or lead CR₄) this electrode is placed in the midclavicular line even when the cardiac apex is far to the left of this position.

galvanometer connections, or to the left leg, which has been much more widely used.*

Multiple Precordial Leads.—In certain cases of infarction of the anterior wall of the heart, multiple precordial leads are required to establish the diagnosis. Such leads sometimes disclose abnormalities of the T-deflection which would otherwise escape detection. In the differentiation of right from left bundle-branch block, and in the differentiation of right from left ventricular enlargement, multiple precordial leads are indispensable. The series of leads particularly emphasized, although not necessarily the best that may be devised, has nevertheless been shown to be of great value and has received sufficient study to establish reasonably adequate normal standards, and to establish the configuration of the changes in the ventricular complex which occur in the different leads of the series as a result of the more common cardiac abnormalities.

In the majority of cases there is no essential difference between the curves obtained when the precordial electrode is paired with an electrode on the left leg and those obtained when it is paired with a central terminal. Essential differences become increasingly common as the distance of the precordial electrode from the ventricular surface is increased.

Method of Making the Galvanometer Connections.—In taking precordial leads the majority of workers in America have hitherto made the galvanometer connections in such a way that relative negativity of the precordial electrode was represented in the finished curve by an upward deflection. Other workers here and abroad have made the galvanometer connections in the opposite way so that relative positivity of the precordial electrode was represented by an upward deflection. It was thought imperative that one or the other method be declared standard. After a great deal of discussion it was decided that the temporary inconvenience to the large number who have become accustomed to

*There is some evidence suggesting that a comparison of Lead IV B and Lead IV F may be useful in the diagnosis of acute pericarditis and of myocardial infarction involving both the anterior and the posterior walls of the left ventricle. Lead IV T seems to be as satisfactory as any of the other apical leads. Compared with the leads in which the apical electrode is paired with a single electrode in the back or on one of the extremities, it is much more nearly unipolar; i.e., it records the potential variations of the precordial electrode without distortion (or with minimal distortion) due to potential variations of the distant electrode. Whether this will prove to be an important advantage from a practical standpoint is as yet uncertain. This lead has the disadvantage that it requires special equipment and is less convenient to use than Lead IV F or Lead IV R. Lead IV L is the most convenient of all because, after Lead III has been taken, a single operation (the transfer of the left leg wire to the apical electrode) is required to obtain it. It has, however, been so little used that it cannot be recommended without reserve at this time. The relative merits of these different leads are in need of thorough investigation. The following relations between them may be pointed out.

$$\begin{aligned}\text{Lead IV R} &= \text{Lead IV F} + \text{Lead II} \\ \text{Lead IV L} &= \text{Lead IV F} + \text{Lead III} \\ \text{Lead IV T} &= \text{Lead IV F} + \frac{1}{3} (\text{Lead II} + \text{Lead III})\end{aligned}$$

These equations are analogous to Einthoven's equation, which states that Lead II = Lead I + Lead III.

the first method would be more than overbalanced by the advantages offered by the second.*

The advantages of making the galvanometer connections in such a way that relative positivity of the precordial electrode is represented in the finished curve by an upward deflection and relative negativity of this electrode by a downward deflection are as follows:

1. This method makes it possible to assign the letters Q, R, and S to the individual deflections of the QRS group in exactly the same manner as in the case of the standard limb leads, without violating the general principle that, as far as possible, deflections which have the same origin or the same significance should invariably bear the same name. In particular, it makes it possible always to assign the same letter (R) to the onset of the intrinsic deflection, which signals the arrival of the impulse at the epicardial surface of the portion of the heart subjacent to the precordial electrode, without departing from the customary method of labelling the QRS deflections.

2. In cases of infarction of the anterior wall of the heart this method yields ventricular complexes characterized by abnormally large initial downward deflections (Q-waves) and sharply inverted T-waves of the "cove plane" or "coronary type." These complexes are practically identical with those which have long been considered characteristic of myocardial infarction in the case of the standard leads, and they may be described in the same terms.

3. The P-deflections and T-deflections are normally upright. There are great advantages, particularly from the standpoint of one who is teaching electrocardiography or of one who is beginning the study of this subject, in a system which makes upright T-waves invariably normal, whatever the lead.

4. The use of the terms plus and minus and of the symbols + and - is greatly simplified. In the case of precordial leads one electrode, the precordial electrode, is much more important than the other. In the discussion of the principles upon which the interpretation of the precordial electrocardiogram rests, it is necessary to refer frequently to the potential of the precordial electrode and in connection therewith to employ the terms and symbols mentioned. Since we are accustomed to speak of downward deflections as negative and to prefix measurements of such deflections with the minus sign, much confusion and misunderstanding will be avoided if the deflection of the trace is upward when the potential of the precordial electrode is positive and downward when the potential of this electrode is negative.

*To make the galvanometer connections in such a way that positivity of the precordial electrode will produce an upward deflection in the finished record, it is necessary to connect the left-hand wire to this electrode if the lead switch is on Lead I and to connect the left-leg wire to this electrode if the lead switch is on Lead II or Lead III. To take Lead IV F, connect the left-leg wire to the precordial electrode and the left-arm wire to the left-leg electrode and place the lead switch on Lead III. To take Lead IV R, connect the left-leg wire to the precordial electrode and the right-arm wire to the right-arm electrode and place the lead switch on Lead II.

Nomenclature.—For the convenience of those who wish to make statistical studies of the QRS group, to measure and tabulate the QRS deflections, or to classify or characterize QRS deflections of different types, it is imperative that the individual deflections of the QRS group be designated by distinct symbols, even though the naming of these deflections may involve the application of rules that are more or less arbitrary.

The adoption in the case of precordial leads of symbols different from those employed in the case of the standard leads might have some advantages. It would, however, have at the same time tremendous disadvantages. It would add an entirely new terminology to clinical electrocardiography which is already regarded by many as an abstruse and incomprehensible subject, and would greatly increase the number of technical terms which beginners in this field would have to learn. It would invite other attempts to improve upon electrocardiographic terminology, and would stand little chance of prompt and universal acceptance. The adoption of new symbols for the initial ventricular deflections would also greatly complicate the use of such terms as the P-R interval, the QRS interval, the RS-T segment, and RS-T displacement which could not then logically be used with reference to precordial leads. For these reasons it was decided that the deflections of precordial leads should be designated by the same letters as those of standard limb leads.

Comments.—In making the recommendations adopted it has been our purpose to simplify the use of precordial leads for those who desire to employ them in everyday clinical work, and to reduce the confusion that exists at present because of a lack of uniformity and precision in current technique and nomenclature. Our discussions have made us acutely aware of many gaps in our knowledge of the precordial electrocardiogram which must be filled in by future investigation. We feel that it would be unfortunate if our attempt to standardize precordial leads should discourage the investigation of leads of any kind whatsoever.

Signed

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Standardization of Precordial Leads

REFERENCE

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Department of Clinical Reports

CORONARY THROMBOSIS IN A CASE OF CONGENITAL DEXTROCARDIA WITH SITUS INVERSUS*

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COMPLETE transposition of the viscera, although uncommon, is of no clinical importance as the organs function in a normal manner. Individuals with this abnormality are liable to be affected by the same diseases as afflict those in whom the organs are in a normal position. The following case of situs inversus is presented because the patient suffered from acute coronary thrombosis and, as far as can be determined, no previous case has been reported of this nature.

CASE REPORT

E. O., a male, fifty-eight years of age, stated that on June 15, 1935 while plastering a wall, he felt his back snap. He developed a severe pain in the lumbar region and slight pain in the chest. He was treated for the back injury which slowly improved but about the middle of July while walking in the street he was seized with severe constricting pain just to the right of the sternum. The pain lasted for about an hour and there was a feeling of numbness in the right arm. Since that time he has had attacks of pain in this situation on exertion or excitement but some have occurred without any apparent cause. They were usually preceded by numbness of the right arm. An attack usually lasted from one-half to one hour but the most severe attack, which took place in September, lasted two hours. There has been no radiation to the left arm or to the neck. He had had slight dyspnea on exertion from time to time but otherwise the history was negative. Patient stated that he had always been right handed. He was admitted to Kings County Hospital on Nov. 20, 1935 and was discharged much improved on Jan. 17, 1936.

Physical examinations revealed a slightly overweight man with some cyanosis of the mucous membranes. The radial and retinal arteries showed sclerotic changes consistent with his age. The pulse was regular at a rate of 68 beats per minute and the blood pressure was 154/84. On examination of the heart the condition of dextrocardia was found, with the apex just outside the right midclavicular line. There was a localized systolic murmur at the apex but no other murmurs were audible. The sounds at the base were faint. There were scattered dry râles on both sides of the chest at the base. The liver was situated on the left side. No edema was present. Routine laboratory studies, including urine, blood, blood chemistry, and Wassermann test, were negative.

Electrocardiograms.—Lead I showed the characteristic features of congenital dextrocardia with inversion of all the complexes; Lead II an inverted P-wave, a deep Q and definite coving of the RS-T segment, with a deep negative T-wave; Lead III a small Q-wave, slight slurring of R, some coving of the RS-T segment followed by a negative T; Lead IV (right arm electrode on apex and left arm electrode just below the angle of right scapula) appeared essentially normal (Fig. 1). The diagnosis was that of previous coronary thrombosis in a case of congenital dextrocardia.

*From the Department of Medicine, Long Island College of Medicine, and the Department of Cardiology, Kings County Hospital.

In order to clarify the situation and make the curves comparable to those usually studied for coronary thrombosis, tracings were made in which the left arm electrode was placed on the right arm, the right arm electrode on the left arm, and the left leg electrode on the right leg (Fig. 2). Lead I was normal except for a slight slurring of R; Lead II showed a small Q-wave and some coving of the RS-T segment with a negative T-wave; Lead III had a diphasic P-wave, a deep Q-wave, marked coving of the RS-T segment and a deep negative T-wave. Were such curves obtained in an individual with the heart in the normal position the diagnosis of a previous coronary thrombosis of the T_2 type with the infarct on the posterior surface of the left ventricle would appear to be justified.

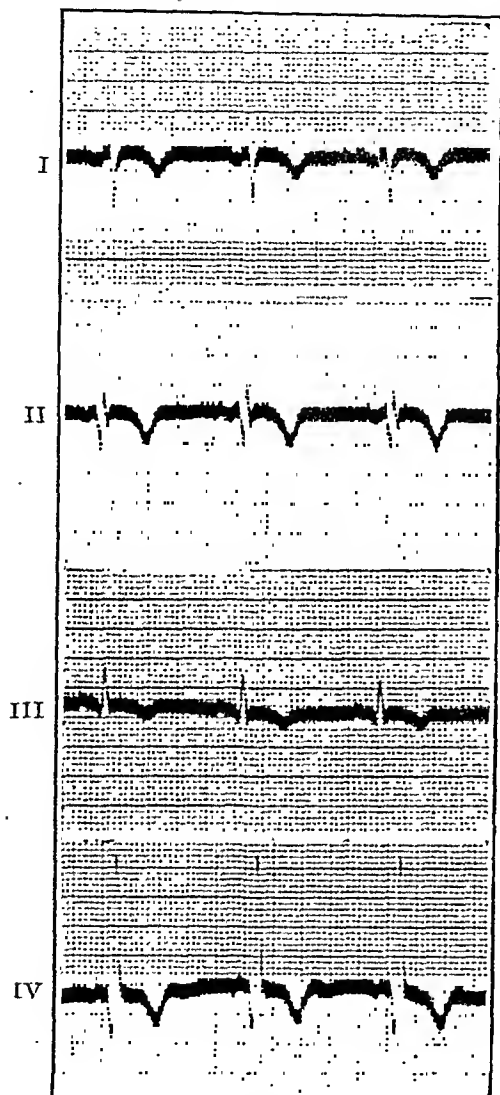


Fig. 1.

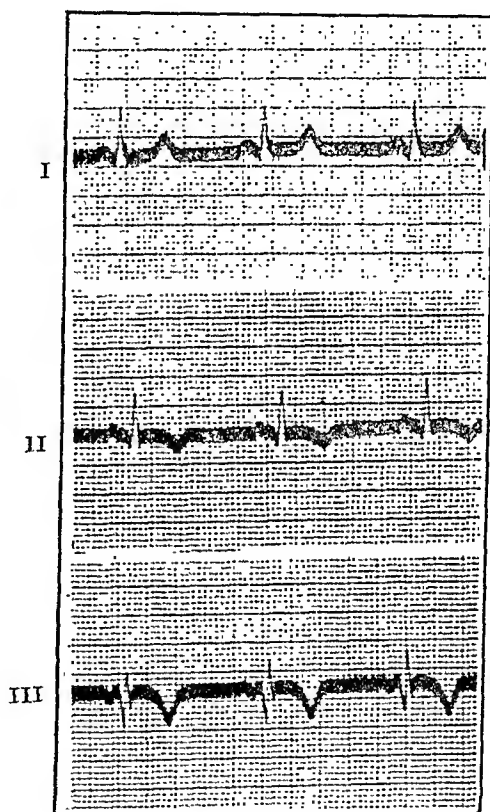


Fig. 2.

Fig. 1.—Standard leads and Lead IV (right-arm electrode-apex, left-arm electrode below angle of right scapula).

Fig. 2.—Left-arm electrode on right arm, right-arm electrode on left arm, and left-leg electrode on right leg.

Roentgenograms.—A six-foot teleroentgenogram of the chest showed dextrocardia with very slight cardiac enlargement (Fig. 3). In order to demonstrate the complete transposition of the abdominal viscera the stomach was filled with barium and a barium enema given (Fig. 4).

SUMMARY

A case of congenital dextrocardia with situs inversus is presented in which there is good evidence that a previous coronary thrombosis had taken place. The most interesting feature is the distribution of the

pain during the attacks of angina pectoris. Before and after the attacks a feeling of numbness appeared in the right arm. The pain was localized strictly to the right side of the chest and there was no radiation to the left arm or neck. When the organs are situated in their normal position the pain is usually localized to the left side of the chest

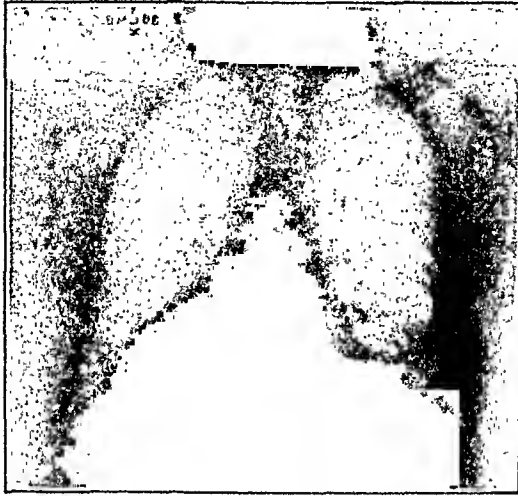


Fig. 3.—Teleroentgenogram of chest at six-foot target distance.



Fig. 4.—X-ray film showing complete transposition of abdominal viscera.

with radiation to the left arm although the pain may sometimes extend to the right chest with radiation to both arms or to the right arm alone. Anatomical evidence shows that the sensory nerve supply from the heart is bilateral and that impulses pass to both sides of the spinal cord. It seems probable however that when the heart is normally situated the main pain pathways run to the left side of the cord while the present case suggests that in dextrocardia they enter on the right side.

SUDDEN DEATH IN AORTIC STENOSIS

EXPLANATION ON A MECHANICAL BASIS*

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IN 1935 Marvin and Sullivan¹ called attention to the fact that patients with stenosed aortic valves are liable to die unexpectedly and suddenly. It had not, until then, been widely known that such a hazard exists in cases of this type, although occasional generalizations on the subject were found in the literature. These investigators reported a group of eleven cases of aortic stenosis in nine of which death had been very sudden when the patients appeared to be in their usual health. Four of the nine did not have heart failure at the time. In four of the cases autopsies were performed, but in only one instance was an apparent cause of the sudden death discovered, namely, a complete closure of the narrowed aortic aperture by a thrombus which was thought to have formed during life. The authors found record of a similar instance of thrombotic obstruction of a stenosed aortic valve ostium in a paper by Lutembacher.² In this case the stenosis had been attributed to rheumatic valvulitis. In all other cases that Marvin and Sullivan found recorded there had been no anatomical findings to explain the sudden death.

These authors reviewed the various possible causes of sudden death, rejecting as improbable such processes as embolic closure of a large artery (coronary or cerebral), or sudden occlusion of the small aortic orifice by a blood clot (at most a rare event if the two cases referred to be considered authentic instances of ante-mortem occlusion). The mechanical narrowing of the aortic orifice is not, of itself, to be regarded as an adequate explanation. They suggest that the size of the heart may be of some importance, since in their cases enlargement of the heart was greater in those patients who died suddenly than in the others. The authors discuss the occurrence of syncopal attacks in five of their patients, three of whom died very suddenly, and advance the idea that both the syncope and sudden death may be due to the cardio-inhibitory action of the carotid sinus reflex.

No subsequent discussion of the subject has appeared in the literature.

The following mechanical explanation of sudden death was arrived at through examination of the heart in a single case of aortic stenosis. The writer has at hand no other material on which to test out his hypothesis, and it is with the hope that others may be in a position to do so, that this report is presented.

*From the Department of Pathology of The Brooklyn Hospital.

CASE REPORT

R. W., a fifty-nine-year-old white male, was admitted to the service of Dr. William H. Lohman at the Brooklyn Hospital on Oct. 6, 1936. Throughout the previous year he had noted dyspnea on exertion and, for the previous two weeks, paroxysmal dyspnea. Physical examination showed pulmonary congestion, the heart enlarged to the left, and the heart sounds of poor quality. There was a systolic thrill and a coarse systolic murmur at the aortic area. The aortic second sound was diminished. The pulse was small and of the plateau type. An electrocardiogram was interpreted as indicating left heart strain. Examination by roentgen ray showed

Fig. 1.

Fig. 2.

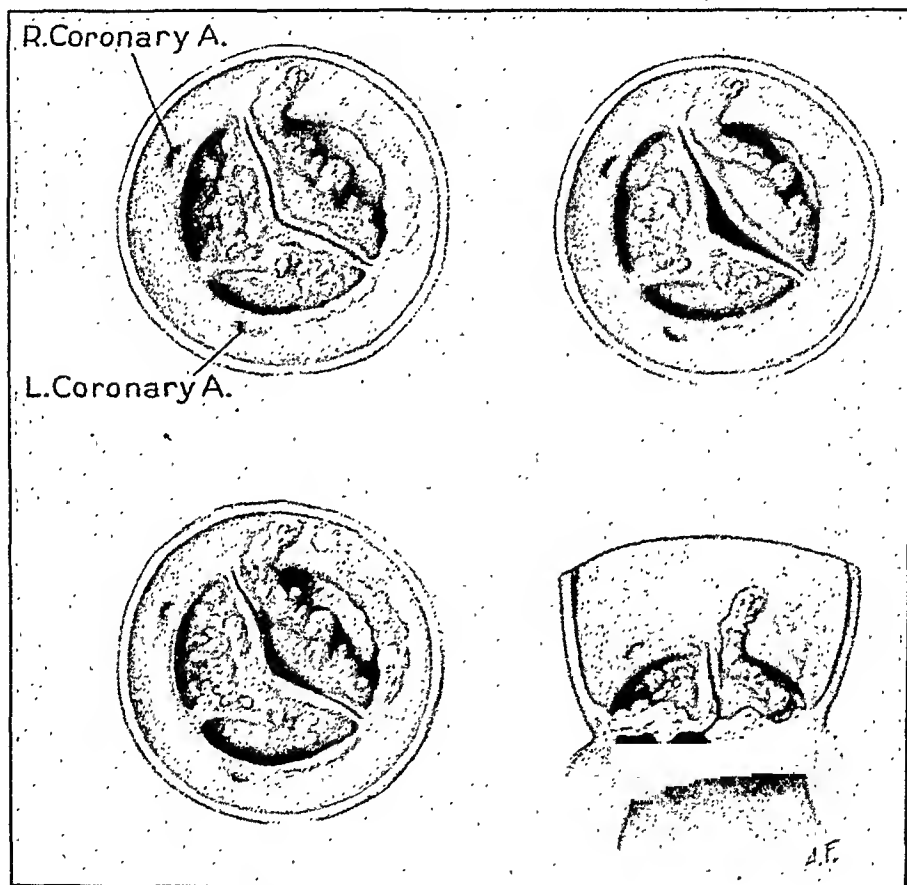


Fig. 3.

Fig. 4.

Fig. 1.—The aortic valve in the position of closure, showing perfect apposition of the edges of the cusps. The fused cusps are each somewhat smaller than the free cusp, simulating a congenital bicuspid valve. Nodular calcareous deposits are seen on the valve and extending onto the aortic wall.

Fig. 2.—The valve in the position assumed during systole. The free cusp is slightly elevated producing a slit-like orifice.

Fig. 3.—The valve in the "locked" position. Slight pressure on the aortic surface of the free cusp served to force it below the margin of the fused cusps. It assumed this position with a little "snap" or click as of a closing door latch.

Fig. 4.—A cross-section through the commissure of the fused cusps and the center of the free cusp. Note the horizontal position of the cusps.

only enlargement of the heart. Renal function was within normal limits. The blood pressure ranged from 170/130 to 175/140. The condition was diagnosed as aortic stenosis on an arteriosclerotic basis. After a stay of four weeks the patient was discharged from the hospital greatly improved and was instructed to report to the clinic.

On Jan. 7, 1937 the patient came to the hospital as a visitor. He spoke animatedly with an interne, who found his pulse to be 90 and remarked on his apparent good health. Ten minutes later, while still at the hospital, the patient collapsed. Within a few moments a physician found him pulseless, with shallow irregular respirations which then ceased. Efforts at resuscitation were of no avail.

At autopsy generalized arteriosclerosis and a moderate degree of chronic passive congestion were found. Other significant pathological changes were confined to the heart, which weighed 650 gm. The pericardium was smooth, thin, and without adhesions. There was enlargement of the entire heart but hypertrophy of the left ventricle was particularly marked. The left ventricular wall measured from 2 to 3 cm. in thickness. There was a relatively great hypertrophy of the musculature of the right ventricle and of the atria, and all of the chambers were moderately dilated. The coronary arteries showed a moderate degree of sclerosis but were not markedly narrowed and contained no thrombi. The tricuspid and pulmonary valves were normal. The mitral valve ring was calcified and there were a few atheromatous plaques on the anterior cusp. There were no adhesions between the cusps and the valve was otherwise normal. The aortic valve was the seat of advanced sclerosis of the Moenckeberg type, with a high grade stenosis. This valve will be described in some detail, since the mechanism suggested as responsible for the sudden death of the patient is based entirely on the condition of the stenotic valve.

All of the aortic cusps were thickened and heavily calcified, and projected rigidly into the lumen of the vessel. The right anterior and left posterior cusps were completely fused. The remaining cusp, the right posterior, was not adherent. The two fused cusps were entirely immobile and formed a kind of shelf occluding about two-thirds of the ostium. The third cusp was also entirely rigid, could be moved but very little and only by virtue of slight flexibility of the wall of the vessel at the base of the cusp. In diastole this free cusp closed the ostium perfectly by resting against the edges of the "shelf" formed by the fused cusps (Fig. 1). In systole it could be lifted slightly to produce an angular, slit-like opening (Fig. 2). It required very little pressure at autopsy to push the free cusp downward under the edge of the shelf, where it remained securely locked (Figs. 3 and 4). More pressure was required to release it than to lock it.

The position of the free cusp at autopsy was not observed until there had been considerable dissection and handling of the specimen, in fact the possibility that such a locking mechanism might have operated as the cause of the sudden death of the patient was not at first considered. It cannot, then, be stated that the valve was found in the locked position, but only that both before and after fixation of the tissue in Klotz solution this mechanism could be demonstrated very convincingly.

The cusps of the valve projected inward from the aortic ring almost at right angles to the wall of the aorta, and the free cusp, therefore, received very little support from the fused cusps during diastole. It seems possible that an unusually forceful diastolic recoil thrust might have served to force the free cusp below the margin of the fused cusps during life, just as it could be pushed down with the examining finger at autopsy.

The writer does not contend that all cases of sudden death in aortic stenosis can be explained by such a mechanism. Obviously it could

operate only with valves showing a type of stenosis similar to the one herein described, the so-called acquired bicuspid valve, and not in cases of complete fusion of the cusps. Satisfactory demonstration of such a mechanism would require careful inspection of the valve prior to the introduction of instruments or examining fingers which would serve to dislodge the locked cusp.

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Department of Reviews and Abstracts

Selected Abstracts

Goormaghtigh, N.: The Structure of the Auricles of the Heart. *Arch. f. Kreislauf-forsch.* 1: 377, 1937.

The auricles of the heart show characteristically many blood filled balloon-like protrusions into the wall. These protrusions can be cut off easily from the heart cavity by the muscle trabeculae which surround their slitlike openings.

KATZ.

Kiese, M., Gummel, H., and Garan, R. S.: The Absorption of G-Strophanthin by the Liver in the Heart-Lung-Liver Preparation. *Arch. f. exper. Path. u. Pharmacol.* 184: 197, 1937.

This was determined by comparing the lethal dose of G-strophanthin in the heart-lung and heart-lung-liver preparation of the dog. When the blood flow of the heart and the liver was about the same per kilo, it was found that the liver took up less G-strophanthin per gram than the heart. It could be shown that liver binding of G-strophanthin was a function of the concentration of the drug in the perfusing blood. Livers damaged by ischemia took up less of the drug than undamaged livers.

KATZ.

Wolf, H. J., Mohr, M., and Kröger, E.: Residual Blood Flow of the Kidney After Ligation of the Main Artery. *Ztschr. f. d. ges. exper. Med.* 100: 485, 1937.

The authors believe from previous work that the production of tyramine has to do with the hypertension which develops after complete ligation of one renal artery. In the present study, the left renal artery was ligated in six dogs. In five, the blood flow from left and right renal veins was measured five to seven days later; in the sixth, one-half hour later. The blood flow was found to be from one-tenth to one-quarter that on the normal side. Secretion of urine did not occur in the kidney deprived of its blood supply. The vessels of the capsule were markedly dilated. This residual circulation is considered to be the source for the transportation of tyramine into the general circulation.

STEELE.

Biehler, W.: Veritol (H 75), a New Circulatory Drug With Peripheral Action. *Ztschr. f. d. ges. exper. Med.* 101: 62, 1937.

β -p-oxyphenyl-isopropylmethylamin marketed under the name of "veritol" was studied by Biehler in cats, rabbits, guinea pigs, and mice. He finds that its action upon arterial pressure lies between that of adrenalin and ephedrin and that its pressor effect is somewhat greater than the related compounds tryamine and hordenine. Intravenously it is effective in approximately $\frac{1}{2000}$ of the lethal dose. It is, furthermore, effective by mouth in rabbits in doses approximately $\frac{1}{80}$ of the lethal dose. Like adrenalin, reversal of the pressor effect occurs after ergotamine and yohimbin. The drug's point of attack, he believes, is both cardiac and peripheral.

STEELE.

Heinlein, H.: Changes in Organs Due to the Substances Native to the Body Which Act Upon the Circulation: I. Histamin. *Ztschr. f. d. ges. exper. Med.* 100: 661, 1937.

The author fed histamin to cats over periods varying from one to three months in quantities sufficient to induce vomiting, as he had previously done with rabbits. He finds histologic lesions chiefly in heart and lungs but to a lesser extent also in liver, spleen, and kidneys. The lesions appear to be dependent upon swelling and breaking down of the intima of the arterioles, fibrin formation beneath, and focal swelling and necrosis of the media. Focal necrosis of the heart and liver was found with leucocytic infiltration and in the kidney marked stasis of the capillary tufts of the glomeruli, protein and occasional red cells in the capsular space with swelling and dissolution of the capsular epithelium. He points out the similarity of these lesions to those obtained in animals made allergic to foreign proteins.

STEELE.

Heymans, C., and Bayless, F.: Concerning the Action of β -p-oxyphenyl-isopropylmethylamine. *Arch. internat. de pharmacodyn. et de thérap.* 56: 319, 1937.

The authors confirm the work of Biehler and of Rein that β -p-oxyphenyl-isopropylmethylamine, a synthetic compound related to tyramine and hordenine, is a mild pressor substance. By means of crossed circulation experiments in donor and recipient dogs they show that its action is due to peripheral vasoconstriction, rather weak in the general periphery, but well marked in the splanchnic region. In the intact animal the pressor effect is very small, as Rein found, because vagal slowing offsets its effect, but in atropinized or vagotomized animals a considerable rise in pressure may occur.

STEELE.

Heymans, C., and Bayless, F.: Influence of Anesthesia by Morphine-Pernoctone and by Chloralosane Upon the Arterial Pressure and Upon the Vasomotor Reflexes of the Proprioceptive Regulation of Arterial Pressure. *Arch. Internat. de pharmacodyn. et de thérap.* 56: 419, 1937.

The effect of closure of both carotid arteries upon arterial pressure carried out in dogs under local anesthesia is compared with the effect of closure of the arteries carried out later in the experiments under (1) morphine-pernoctone and (2) chloralosane anesthesia. The results show that the former tends to depress markedly arterial pressure as well as the means of regulating it while the latter does not. He concludes that Rein's statements that morphine-pernoctone does not influence any of the known vasomotor reactions is unjustified and that chloralosane is a very suitable anesthetic for studies of the physiology of the circulation.

STEELE.

Katz, Louis N., and Feil, Harold S.: Clinical Observations on the Dynamics of Ventricular Systole. IV. Pulsus Alternans. *Am. J. M. Sc.* 194: 601, 1937.

The dynamics of systole in five clinical cases of pulsus alternans were studied by optical registration methods. The following conclusions were reached:

The alternation in the size of the pulse is accompanied by concordant alternations in the heart sounds, the gradient of the pulse and the duration of ejection, and by a discordant alternation in the duration of the isometric period. The duration of total systole showed no alternation.

No alternations were found in the electrocardiograms in this series, although conduction disturbances were present in four of the cases.

The duration of diastole did not vary consistently and was so small as to be without significance in explaining the alternation of the pulse volume.

In the case with complete heart-block the pulsus alternans is attributed to contribution of auricular stimuli in alternate diastoles.

The evidence presented in this report, when correlated with previous studies of the dynamics of systole, supports the view that changes in initial volume and tension such as follow extrasystoles and sudden changes in rhythm and in respiration (so often present in alternation) can help to initiate the phenomenon of pulsus alternans. Once established, alternate variations in systolic residue occur which alternately increase and decrease the initial tension and volume and so help to perpetuate the phenomenon. It is not denied that changes in the refractory phase are important in initiating and perpetuating pulsus alternans, but it is emphasized that the changes in initial tension and volume are likewise important.

AUTHOR.

Steinberg, Israel, Clark, Eugene, and de la Chapelle, Clarence E.: Suppurative Pleuritis Complicating Pulmonary Infarction in Congestive Heart Failure. *Am. J. M. Sc.* 194: 610, 1937.

In the foregoing report are presented the clinical and necropsy findings in four patients with congestive heart failure, in whom suppurative pleuritis complicated pulmonary infarction. The evidence discussed indicates that bland pulmonary infarcts may spontaneously undergo secondary infection which leads to empyema by penetration of the microorganisms to the pleura.

AUTHOR.

Wilkins, Robert W., Weiss, Soma, and Haynes, Florence W.: The Effect of Epinephrin in Circulatory Collapse Induced by Sodium Nitrite. *J. Clin. Investigation* 17: 41, 1938.

The effect of epinephrine has been studied in vasomotor collapse induced by sodium nitrite in subjects in the upright position.

Both in the horizontal and in the upright positions, epinephrine in subcutaneous doses of 1 mg. caused arteriolar constriction in and decreased blood flow through the hand. The venous tone was increased, as was the arterial pulse pressure and the heart rate; the venous pressure was usually slightly elevated.

Epinephrine did not prevent the vasomotor collapse and syncope produced by sodium nitrite, mainly because the arteriolar constriction and the tissue anoxia were enhanced and because the decreased venous tone produced by nitrite was not adequately compensated for.

The experiments indicate that the level of the arterial pressure is not a reliable index of the clinical manifestations of vasomotor collapse or of the degree of tissue anoxia.

The study presented throws light on the treatment of different types of vasomotor collapse. The fact that epinephrine is ineffective in nitrite collapse does not rule out its efficacy in other types of collapse.

AUTHOR.

Vannotti, A.: The Capillaries and Nourishment of the Heart and Large Vessels Under Normal and Pathologic States—I and II. *Ztschr. f. d. ges. exper. Med.* 99: 158 and 371, 1936.

Benzidine coloring of erythrocytes was used to study the flow in the smallest vessels in the heart muscle during systole and diastole. A brisk circulation was found to occur during systole. The number of functioning anastomoses decreased.

Toward the end of systole there is a hindrance to venous flow. In diastole there is dilatation of the smallest vessels and the appearance of a rich anastomotic network. The picture is the same on the outer and inner layers of the heart. No evidence exists of an extravascular compression of the capillaries during systole. The systolic flow is maintained by elevation of the coronary arterial pressure and the arteriole widening in this phase.

In cardiac hypertrophy there is a noticeable increase in the number of active capillaries and vicarious anastomoses, while in dilatation there is a diminution of the normal blood flow and an increase in the anastomotic circulation.

KATZ.

Vannotti, A.: The Capillaries and Nourishment of the Heart and Large Vessels Under Normal and Pathological States—III. *Ztschr. f. d. ges. exper. Med.* 99: 387, 1936.

In diphtheritic myocarditis of the guinea pig heart, one finds first a myocardial active hyperemia and then an ischemia when fatty degeneration of the heart occurs. Around these ischemic areas new capillaries appear which indicate the onset of the reparative stage.

KATZ.

Vannotti, A.: The Capillaries and Nourishment of the Heart and Large Vessels Under Normal and Pathological States—IV. *Ztschr. f. d. ges. exper. Med.* 99: 557, 1936.

Diffusion of vital dyes occurs normally through the endocardium of the aorta and through the capillaries of its adventitia. In hypertension there is a decrease in the latter diffusion and an increase in the transintimal diffusion. Histologically, one can also demonstrate medial necrosis and calcification. Apparently only in the valves and auricles is endocardial diffusion adequate to nourish underlying structures, but this is not the case in the aorta.

KATZ.

David, F., and Siedek, H.: Bloodless Method of Measuring Pressure in the Pulmonary Artery. *Ztschr. f. d. ges. exper. Med.* 100: 54, 1936.

With a bronchoscope, one can see pulsations in the right bronchus 1 cm. below the bifurcation of the trachea. A small rubber balloon is adjusted to cover this region, and the pulsations recorded with varying pressures within the balloon. The oscillograms permit the determination of the pressure on Marey's principle. In twenty dogs this pressure was found to be 30 per cent of the systemic. In two experiments the author found a favorable comparison between the indirect and the direct measurements. In man the author found a similar relation between pulmonary and systemic pressure.

KATZ.

Blumgart, Herrman L., Hoff, Hebbel E., Landowne, Milton, and Schlesinger, Monroe J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries in Producing Persistent Electrocardiographic Changes. *Am. J. M. Sc.* 194: 493, 1937.

Since, according to current belief, angina pectoris and cardiac infarction are the result of myocardial ischemia, experiments were undertaken to learn whether temporary interruption of the blood supply to a portion of the heart would result in persistent electrocardiographic or anatomic changes.

Occlusion of the left anterior descending coronary artery or one of its branches for from five to forty minutes with subsequent release of traction was performed in twenty-four cats. Twenty-one animals were allowed to survive for from one to nine days after this procedure.

Electrocardiograms of the three conventional leads obtained before and at various intervals during and following occlusion revealed anoxic changes persisting during the postoperative days in all animals in which occlusion was maintained for from fifteen to forty minutes, inclusive. Only three of six animals in which the period of occlusion was ten minutes or less showed changes on the postoperative days; in one these changes persisted until sacrifice of the animal eight days post-operatively. The electrocardiographic changes were characteristic of the anterior infarction type.

Post-mortem examination failed to reveal gross or histologic evidences of cardiac infarction in any instance.

Cardiac irregularities consisting of ventricular extrasystoles and ventricular fibrillation were observed at times during occlusion but particularly on release of traction. Three of the five animals which developed ventricular fibrillation died immediately.

The clinical counterparts of these experimental observations are discussed.

AUTHOR.

Draper, George, Bruenn, Howard G., and Dupertuis, C. Wesley: Changes in the Electrocardiogram as Criteria of Individual Constitution Derived From Its Physiological Panel. *Am. J. M. Sc.* 194: 514, 1937.

A precision method has been used to study a constitutional character in the physiologic panel.

There is a high degree of constancy over long periods of time in the individual electrocardiographic pattern demonstrated in one or both of (a) an unchanging pathologic state (Einthoven) and (b) the circumstance of a continually normal heart.

Significant differences between the electrocardiographic curve patterns for ulcer and gallbladder patients appear to exist within certain age groups.

These differences are also significantly distinct from the electrocardiograms of individuals with normal records selected from a general hospital population.

AUTHOR.

Lucke, H.: Cardiac Arrhythmias of Central Origin. *Deutsches Arch. f. klin. Med.* 180: 40, 1937.

Two cases are reported, one of cerebral confusion (*commotio cerebri*) and the other of brain stem involvement, in which cardiac arrhythmias of vagal origin (since atropin tended to abolish them) occurred. In one case the arrhythmia was in the nature of extrasystoles and in the other there was sinus bradycardia and arrhythmia, multiple ectopic beats, and first and second degree A-V block.

KATZ.

Tochowicz, L.: The Clinical Value of the Dorsoventral Lead. *Ztschr. f. Kreislauf-forsch.* 29: 711, 1937.

In 280 cases with stenocardia, it was found that using four leads increased the electrocardiographic evidence from 50 per cent, obtainable with the limb leads alone, to 80 per cent when the fourth lead is added. This the author states is one of the reasons this lead is valuable.

KATZ.

Bloch, C.: Resemblance in the Appearance of Automatic and Extrasystolic Beats. *Cardiologia* 1: 186, 1937.

Six cases are reported in which extrasystoles and automatic beats had the same electrocardiographic contour and the pauses between the automatic beats were multiples of the extrasystolic coupling. These rhythms occurred in cases with serious heart disease, or following digitalis, carotid sinus pressure or exercise. These two types of beats are from the same focus. The presence of "exit" block is important in this mechanism and relates it to parasystole.

KATZ.

Boyd, Linn J., and Werblow, S. Charles: Coronary Thrombosis Without Pain. *Am. J. M. Sc.* 194: 814, 1937.

Additional evidence is submitted to support the idea that major coronary thrombosis may occur without pain. Pain was not present in one-third of 127 cases of coronary thrombosis observed by the writers during a twenty-five-month period although its occurrence was the subject of particular inquiry.

Seven cases of this type are reported briefly. The occurrence of three cases in females among 7 reports is suggestive of the increasing occurrence of coronary thrombosis in women. Although Metropolitan Hospital has a large negro clientele, only 1 colored patient is reported, and he was the son of a white father and half-white mother.

Most of the cases were known to be cardiac and had manifested more or less cardiac failure for periods varying from a few weeks to many years. Sudden inexplicable increased congestive failure in a known cardiac patient should arouse suspicion of coronary thrombosis; moreover in such cases pain is usually absent. There was 1 case of a pain equivalent in the form of "choking," several of severe vertigo, commonly associated with periods of unconsciousness, and 1 of a painless episode in the so-called "digestive" group.

The diagnosis of painless coronary thrombosis, as a rule, should not be difficult if the possibility is considered. Our mistakes have occurred mainly in elderly individuals with known arteriosclerotic heart disease and hypertension.

Painless coronary thrombosis probably occurs more frequently than is generally appreciated, and we may assume that mild cases are more common than the fatal examples reported in this paper.

As the histories of these patients are singularly free from pain, they may belong to Libman's hyposensitive group. It is suggested that greater attention should be paid to the nerve plexuses surrounding the coronary vessels in cases of painless coronary infarction.

AUTHOR.

Levy, Robert L., and Golden, Ross: Roentgen Therapy of Active Rheumatic Heart Disease. A Summary of Eleven Years' Experience. *Am. J. M. Sc.* 194: 597, 1937.

Forty-eight patients with rheumatic heart disease have been treated by roentgen irradiation of the heart and have been observed during the past eleven and one-half years.

In a considerable number the evidence indicated that radiation therapy exerted a favorable effect upon the lesions in the heart and upon the course of the disease. Those receiving the larger number of treatments, as a general rule, fared best.

Irradiation relieved cardiac pain in patients who did not have aortic insufficiency.

No harmful effects were noted. Unpleasant radiation reactions appeared in about half the cases.

Cases with low grade activity and without signs of congestive heart failure appear to be most benefited.

The manner in which improvement is initiated is not known. It is believed to be due to an altered response of the cardiac tissues induced by the rays.

Roentgen irradiation of the heart, in the present state of knowledge concerning rheumatic fever, deserves a place as a therapeutic measure in properly selected cases of active carditis.

AUTHOR.

Dawson, W. S.: Cerebral Arteriosclerosis: A Review. *Australia* 2: 499, 1937.

While arteriosclerosis may be inferred with a fair degree of certainty when mental deterioration, with or without focal signs, occurs in the subject of general arteriosclerosis, in many more cases the existence of this pathologic change can be suspected only during life, and final proof depends upon the results of microscopic examination. Even so, the older the patient, the greater will be the probability, that simple neuronic decay is the major factor in the clinical condition, with the reservation that cerebral arteriosclerosis cannot be excluded until the brain has been examined microscopically.

AUTHOR.

Wollheim, E.: A New Depressor Substance and Its Relation to the Pathogenesis of Essential Hypertension. *Schweiz. med. Wehnschr.* 66: 1231, 1936.

A new thermostable depressor substance, not related to other depressor substances, was obtained from the human urine, horse's urine, and the posterior lobe of the pituitary gland of the cow. The author calls this substance depressan and finds that it is related to human essential hypertension, in that it is absent in the urine of hypertensive subjects. He concludes that hypertension is the result of a deficient production of this substance.

KATZ.

Wallis, O.: Action of Folliculin on the Blood Pressure. *Zentralbl. f. Gynäk.* 60: 2839, 1936.

In 12 cases of essential hypertension (8 females and 4 males), the follicular hormone had no depressor action.

KATZ.

Dozzi, Daniel L.: Cerebral Embolism as a Complication of Coronary Thrombosis. *Am. J. M. Sc.* 194: 824, 1937.

One thousand consecutive, unselected autopsies were analyzed for the incidence of cerebral embolism and cerebral thrombosis in patients known to have coronary thrombosis. The same series was then analyzed for the incidence of unsuspected coronary thrombosis in cases with a clinical diagnosis of cerebral hemorrhage, cerebral thrombosis, and cerebral embolism.

Of the 1,000 patients, brains of 138 were examined at autopsy. Of these, 107 had either cerebral hemorrhage, cerebral thrombosis, or cerebral embolism. Of these 107 coronary thrombosis also occurred in 12 cases (11.2 per cent). The latter lesion was not diagnosed clinically in a single case and suspected in only 2.

While there were 41 cases of coronary thrombosis in the series of 1,000 autopsies, only 29 of these were clinically recognized and recorded. The remaining 12 were found as clinically unsuspected coronary thromboses in the autopsy records of the 107 cases that had a clinical diagnosis of either cerebral hemorrhage, cerebral

thrombosis, or cerebral embolism. None of the 29 cases clinically recognized was shown to be associated with a cerebral lesion. The association of 12 of the 41 cases of coronary thrombosis with a cerebral vascular lesion gives an incidence of 29 per cent, a higher figure than those found in the literature.

Though this series is too small to permit definite conclusions, this indication of a high incidence of unsuspected coronary thrombosis in cases of hemiplegia should serve as a stimulus for more extensive study and investigation.

As a result of the findings of this study, the following suggestions present themselves:

1. While it is generally felt that the heart is frequently the source of a cerebral embolus in persons under forty years, it would be wise to suspect the heart in all cases of cerebral embolism, irrespective of the patient's age.

2. When suspecting the possibility of coronary thrombosis as the etiologic factor in a case of hemiplegia, we must bear in mind the atypical forms of coronary thrombosis and must not lose sight of the fact that in cases with congestive heart failure the coronary thrombosis might be masked by dyspnea.

All cases of hemiplegia should have a careful search made for any clue leading toward old or recent coronary thrombosis in addition to routine electrocardiographic tracings.

4. In order to establish the true incidence of cerebral embolism or cerebral thrombosis as a sequel of coronary thrombosis, we must examine the heart at autopsy in all cases that clinically have a cerebral lesion. Also we must examine the brain in all cases with coronary thrombosis with any neurologic manifestations.

AUTHOR.

Prettin, F.: Thrombosis and Fatal Lung Embolism. Virchows Arch. f. path. Anat. 297: 535, 1936.

A study based on necropsy material shows that postoperative fatal lung embolism occurs especially in abdominal operations, most often from the third to the eighth postoperative day. The primary thrombi were located most often in the inferior vena cava, iliac veins, femoral veins or prostatic or uterine plexus. Deaths were more frequent over the age of forty and increased with age. In 135 out of 229 cases, marked arteriosclerosis of the heart and blood vessels was found. Women with this condition were on the average 11 kilos over the average normal weight and men on the average 4.2 kilos overweight. Two-thirds of all cases were not diagnosed clinically.

KATZ.

Brown, Margaret E.: The Occurrence of Arteriovenous Anastomoses in the Tongue of the Dog. Anat. Rec. 69: 287, 1937.

As compared with the arteriovenous anastomoses described by Masson in the human, those found in the dog's tongue are relatively simpler though they agree in their fundamental characteristics. It is suggested that their presence in the dog's tongue may be connected in some way with the elimination of heat upon a rise in body temperature. As far as the author is aware arteriovenous anastomoses have never been seen in the tongue of any other of the laboratory animals.

MONTGOMERY.

Pearl, Felix L.: Angiospastic Claudication: With a Report of Six Cases. Am. J. M. Sc. 194: 505, 1937.

Treatment should be conservative. If this fails, the response to diagnostic novocaine block will determine the advisability of lumbar ganglionectomy. The

latter procedure should be advised patients who are good risks, are incapacitated by the symptoms, and are relieved by diagnostic block. If vasomotor studies show receding of the vasodilatation level, lumbar ganglionectomy should be done. Poor surgical risks may be treated by alcohol injection of the lumbar sympathetic chain.

The term "angiospastic claudication" is descriptive of the syndrome and distinguishes it from the claudication of occlusive arterial disease.

AUTHOR.

Schlomka, G., and Broich, W.: The Physiologic Variations in Heart Size. Arch. f. Kreislaufforsch. No. 1, 384, 1937.

Roentgenkymography shows that the heart size is not so constant as distant heart plates seem to indicate. A shift of 3.5 to 4 mm. in transverse diameter is not unusual during the heart cycle and in 20 per cent of the cases exceeds 6 mm. and not so uncommonly even 10 mm. The size of the heart both systolic and diastolic varies inversely with heart rate, viz. slowing increases and acceleration decreases it. Increasing diastolic arterial pressure usually causes a decrease in transverse diameter of the heart, and a decrease in pressure causes an increase in diameter. An increase in body weight increases the heart diameter irrespective of the position of the diaphragm. Elevation of the diaphragm readily causes significant increases in the transverse diameter of the heart. These results suggest that kymography should be used as the standard method of measuring heart size and that this be done during moderate respiration.

KATZ.

Raab, W.: Adrenals and Angina Pectoris—Pathogenesis and Roentgentherapy. Arch. f. Kreislaufforsch. No. 1, 255, 1937.

In angina pectoris, except for those cases due to acute coronary closure and other rare forms, the attacks are brought on by the outpouring of adrenalin. Twenty typical cases of angina pectoris are presented in which roentgentherapy of the adrenals was used, apparently successfully, to relieve the attacks.

KATZ.

Ratschow, M.: Vasography as a Test of the Function of the Peripheral Blood Vessels. Fortschr. a. d. Geb. d. Röntgenstrahlen. 55: 253, 1937.

After the needle is inserted into the lumen of an artery, the flow is stopped for five minutes and then started again while injecting the contrast material. This causes dilatation of all channels and permits visualization of all dilatable vessels. This can also be accomplished by novocaine block of the nerve. Diathermy permits visualization of local regional vessels. The time from the injection until the constant medium leaves the veins is a valuable measure diagnostically. The injection of a contrast medium into a lymph node permits visualization of lymph channels. The use of a contrast medium has permitted the author to demonstrate by means of changes in vein caliber that systolic acceleration of the venous flow occurs in the large systemic and the large lung veins.

KATZ.

White, James C.: Progress in the Surgery of the Autonomic Nervous System. New England J. Med. 217: 660, 1937.

This is an important eight-page summary, the greater part of which is devoted to a discussion of the effect of autonomic nerve regulation of blood supply. It gives physiologic interpretations as well as useful information of a clinical sort.

Examples are the following: Hemiplegia results in an increase in blood flow in the paralyzed limb, and this may go on to edema of the limb. Preganglionic thoracic sympathectomy is a satisfactory method for production of vasodilatation in the arms—as satisfactory as the older operation of the same sort for the lower extremities. The peripheral vasoconstriction resulting from the use of tobacco does not take place after appropriate sympathectomy. Resection of stellate ganglion for angina pectoris has been followed by a high proportion of favorable results.

The carotid sinus syndrome and some rare but striking vasomotor syndromes of cerebral origins are discussed. Results of various surgical methods for reduction of hypertension are given. An extensive bibliography helps to make this paper a valuable help to a clinician interested in the newer findings in neurologic control of the circulation.

MONTGOMERY.

Duggan, Walter F.: Treatment of Tobacco Amblyopia With Vasodilators. J. A. M. A. 109: 1354, 1937.

In cases of tobacco amblyopia without optic atrophy, the visual improvement obtained with intramuscular injections of acetylcholine chloride roughly paralleled that obtained with intravenous injections of sodium nitrite.

Visual improvement was more rapid in the patients treated with acetylcholine, but it was greater in the patients treated with sodium nitrite.

The vision of the individual eyes was on the whole more reduced before treatment (more eyes had vision of 20/70 or less) and were on the whole better after treatment (more eyes had vision of 20/30 or better) in the patients treated with acetylcholine. For this reason it would seem that intravenous injections of sodium nitrite are more effective than intramuscular injections of acetylcholine chloride in the treatment of tobacco amblyopia.

This slight but definite difference in potency is probably due to the fact that sodium nitrite is destroyed, inactivated, or excreted by the body less rapidly than acetylcholine, so that its vasodilating effect is active for a longer time.

The conclusion seems unavoidable that either sodium nitrite or acetylcholine, administered parenterally, brings about a more rapid return of vision in cases of tobacco amblyopia without optic atrophy than has been shown to occur in comparable series of cases as a result of treatment with time honored but relatively ineffective methods or drugs. This fact should lend additional support to the hypothesis that tobacco amblyopia is due primarily to a vascular spasm in the visual pathway.

AUTHOR.

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IMMUNIZATION AGAINST RHEUMATIC FEVER WITH HEMOLYTIC STREPTOCOCCUS FILTRATE*

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THIS paper discusses an attempt to immunize 34 children who have had one or more attacks of rheumatic fever with stock filtrate of *Streptococcus hemolyticus*. The procedure was suggested by a similar method used by Dr. Franklin Stevens in treating bacterial asthma and arthritis in adults at the Presbyterian Hospital.

We realize that the number of patients treated is too small to be able to draw definitive conclusions, but the results appear significant enough for a preliminary report, in the hope of stimulating research along similar lines.

The treated patients, designated here as Group A, are divided into two groups. Ten children received inoculations with the filtrate from September 1933 to June 1935 (Group A1),† and 24 other children from September 1935 to June 1937 (Group A2).

In each instance 34 patients were used as controls (Groups B1 and B2). These controls were examined regularly in the rheumatic fever and cardiac clinics and received standard treatment as complaints arose, but no attempt was made to immunize them.

According to Stevens‡ it requires approximately two years to treat a case of bacterial asthma. We decided to apply the same tentative rule to patients with rheumatic fever.

Preparation of the Filtrate.—Stock filtrate only was used. A strain of scarlatinal streptococcus N.Y.5 was obtained through the courtesy of Dr. Franklin Stevens and was used exclusively in the preparation of the material. The bacteria were grown for four days in 50 c.c. of 2 per cent proteose peptone broth. The material was filtered; the filtrate was tested for sterility, and four normal saline dilutions were set up: 1:100, 1:50, 1:20, and 1:5. Some undiluted filtrate was kept for the largest doses.

*From the Department of Pediatrics, Fifth Avenue Hospital, 1933-35, and the Department of Cardiology, Flower-Fifth Avenue Hospital, 1935-37.

†Reported before the Pediatric Section of the Medical Society of the County of New York, March, 1936.

‡Personal communication, 1933.

Mode of Administration.—Subcutaneous injections were first given weekly in graduated doses of 0.3, 0.6, 0.9 c.c. beginning with the 1:100 dilution, followed by similar doses of stronger concentrations. After 12 injections, a month was allowed to elapse, at the end of which time 0.3 c.c. of the full strength filtrate was given, followed at monthly intervals by 0.6 and 0.9 c.c. The latter dose was repeated monthly until the beginning of June. The treatment was then discontinued until September when the whole course was repeated as before. No more than a local reaction with the larger doses was ever observed.

CHOICE OF PATIENTS

The only criterion used for selecting the patients for treatment was their willingness to cooperate during the protracted course of inoculations, involving weekly and monthly visits to the clinic. Age, sex, and the severity of the disease played no part in our choice.

The control Group B consisted either of patients whose parents for some reason could not or would not bring them to the clinic frequently and regularly, or of those who joined the clinic too late to receive the full course of treatment. On the whole the cooperation of the families was remarkably good, and only two patients in the control Group B2 disappeared in the course of two years.

Half of the patients were Italian, one-quarter Puerto Ricans, and the rest were mostly Irish, Jewish, or American Negro. The economic and educational status of the majority was low.

ROUTINE PROCEDURE AT THE CLINIC

To evaluate the results of the therapy it is necessary to know about the routine "work-up" of each patient. On admission a detailed history was taken consisting of past, rheumatic, family, racial, and hygienic histories. A careful inquiry was made into the child's habits and mental and emotional make-up.

Each patient was then tested with hemolytic streptococcus nucleoprotein to determine his sensitivity to the organism, followed by a blood count, erythrocyte sedimentation rate, and throat culture for predominating organisms. The parents received printed instructions in English, Spanish, or Italian telling how to deal with a child with rheumatic fever. Each patient was examined regularly at the heart clinic. The assistance of the social service department was invoked whenever necessary.

At each subsequent visit the interval history was taken, a throat culture and sedimentation rate done, and a blood count as often as possible. Whenever subacute rheumatic symptoms or an upper respiratory infection presented itself the child was sent home to bed and was reexamined a week later. In case of a frank attack of rheumatic fever the patient was often admitted to the ward. Convalescent care was arranged for as many children as possible.

DISCUSSION OF RESULTS

For clarity's sake we will first compare the results in Group A1, comprising 10 children treated over the period of two years, from September 1933 to June 1935, with its control group of 34 patients, designated as B1, and then the group of 24 children, called Group A2, whose treatment lasted from September 1935 to June 1937, with its corresponding control Group B2.

Table I gives the comparison between Groups A1 and B1 before the treatment was instituted, and Table II does the same for Groups A2 and B2. Tables III and IV represent the findings in the treated and the control groups respectively during each two-year course of immunization. In Tables V and VI we place under "results" our estimate of the child's physical condition from the general and the rheumatic fever point of view at the end of each two years of therapy.

TABLE I
COMPARISON OF GROUPS A1 AND B1 BEFORE TREATMENT

	TREATED GROUP					CONTROL GROUP				
	10 8.7 yr.					34 9.47 yrs.				
No. of patients										
Average age										
Sex	Males		Females			Males		Females		
Cardiac class	5		5			11		23		
number	F, E+F, I, IIa, IIb					F, E+F, I, IIa, IIb				
History of acute rheumatic fever	2		1			9		7		
Positive skin test	7,		70 per cent			19,		56 per cent		
	10,		100 per cent			27,		79.5 per cent		

TABLE II
COMPARISON OF GROUPS A2 AND B2 BEFORE TREATMENT

	TREATED GROUP					CONTROL GROUP				
	24 7.2 yr.					32 8.5 yr.				
No. of patients										
Average age										
Sex	Males		Females			Males		Females		
Cardiac class	11		13			15		17		
number	F, E+F, I, IIa					F, E+F, I, IIa, IIb				
History of acute rheumatic fever	9		7			8		12		
Positive skin test	19,		All			28,		All		
			70.9 per cent					87.5 per cent		

Group A1.—Ten children are included in this group. Their average age was 8.7 years at the time the treatment was begun in September 1933. The sexes were equally divided. Two children had severe heart disease (Cardiac Class II). In the course of treatment during the following two years the average erythrocyte sedimentation rate* and hemoglobin percentage were 10.5 mm. and 75 per cent, respectively. As far as infections are concerned there has not been a single instance

*Landou's microsedimentation method was used exclusively on ambulatory patients. The normal findings are up to 8 mm. per hour.

TABLE III

COMPARISON OF GROUPS A1 AND B1 DURING TREATMENT SEPTEMBER 1933-JUNE 1935

	TREATED GROUP			CONTROL GROUP		
Average erythrocyte sedimentation rate	10 mm. per hr.			13 mm. per hr.		
Average hemoglobin per cent	75			72		
Total number of colds	28			77		
No. of colds per child	2.8			2.57		
No. of rheumatic fever attacks	0			7 in 5 patients		
Hospitalization	2			15		
Convalescent care	2			3		
Pallor	3+,*		1+++	7+,	7+ +,	9+ + +
Abdominal symptoms	4+,	1+ +,	1+ + +	9+,	3+ +,	9+ + +
Headaches			1+ + +	8+,	6+ +,	6+ + +
Epistaxis	2+			5+,	6+ +,	4+ + +
Rheumatic pains	3+,	2+ +,	1+ + +	6+,	8+ +,	9+ + +
Average gain in weight	15.5 lb.			6.82 lb.		
* +, occurred once						
+ +, occurred twice						
+ + +, occurred many times						

TABLE IV

COMPARISON OF GROUPS A2 AND B2 DURING TREATMENT SEPTEMBER, 1935-JUNE, 1937

	TREATED GROUP			CONTROL GROUP		
Average erythrocyte sedimentation rate	8.5 mm. per hr.			11 mm. per hr.		
Average hemoglobin per cent	80			76		
Total number of colds	103 for 20 patients			130 for 23 patients		
Chronic sinusitis	4, at the end 2			9		
Average number of colds	4.2			5.6		
Number of rheumatic fever attacks	2			17 in 14 patients		
Hospitalization	1			7		
Pallor	3+,*	2+ +,	4+ + +	5+,	3+ +,	10+ + +
Abdominal symptoms	9+,	3+ +,	2+ + +	8+,	10+ +,	9+ + +
Headaches	2+,	5+ +,	4+ + +	5+,	5+ +,	18+ + +
Epistaxis	2+,	4+ +,	1+ + +	2+,	4+ +,	9+ + +
Joint and muscle pains	7+,	4+ +		3+,	6+ +,	18+ + +
Average gain in weight	10.9 lb.			10.5 lb.		
* +, occurred once						
+ +, occurred twice						
+ + +, occurred many times						

TABLE V

	GROUP A1 RESULTS OF TREATMENT		GROUP B1 CONTROL	
	10 cases		34 cases	
Very good	9	90 per cent	5	14.7 per cent
Good	1	10 per cent	9	23.5 per cent
Fair	0	0	10	25.9 per cent
Poor	0	0	10	25.9 per cent

TABLE VI

	GROUP A2 RESULTS OF TREATMENT		GROUP B2 CONTROL	
	24 cases		32 cases	
Very good	17	70 per cent	5	15.8 per cent
Good	4	17 per cent	10	31 per cent
Fair	2	8.9 per cent	5	15.8 per cent
Poor	1	4.1 per cent	12	37.4 per cent

of acute rheumatic fever during the entire course of treatment and there were 2.8 other infections per child, including colds, a case of lobar pneumonia, and a case of otitis media. The average gain in weight per child for two years was 15.5 pounds.

Abdominal symptoms were almost absent. Only one child during the first year complained of frequent abdominal pain. Pallor was observed in four patients and was marked in one. One child complained of headaches which disappeared as soon as an old sinus infection was effectively treated in the ward. Three patients reported joint pains on one transient occasion, two on two occasions and one frequently. No twitching or nervousness was observed in this group. There has not been a single hospital admission for rheumatic fever, but there was one for pneumonia and one for sinusitis. Two children received convalescent care.

Group B1.—Thirty-four children were included in this group. They were all registered in the clinic on an average for thirteen months. The mean age at the time of enrollment was 9.57 years. Eleven of the patients were boys and 23 girls. Nine children, or 25 per cent, were in the cardiac Class II, i.e., they had severe heart disease. Nineteen children (56 per cent) had a history of one or more attacks of rheumatic fever, and seven had had chorea (all with one exception in combination with other rheumatic equivalents), and the remainder of the eight children gave a history of rheumatic symptoms without definite attacks of rheumatic fever. The average sedimentation rate and hemoglobin percentage for the total time of observation were 13 mm., and 72 per cent respectively. Thirty children reported 77 colds and four had chronic sinusitis and were never free from colds. Excluding the cases with sinusitis this makes 2.57 colds per child. The mean gain in weight per patient was 6.82 pounds.

Abdominal pain and vomiting were reported in 23 patients and in nine of them the symptoms were frequent and severe. Twenty-one children also showed pallor, often to a marked degree, 20 complained of headaches (severe in six), and 15 had epistaxis on one or more occasions. Joint and muscle pains occurred in 23 patients. There were seven attacks of acute rheumatic fever in five children. There were 15 admissions to the hospital in this group and three patients were sent to the country for convalescent care.

Group A2.—The results of the first two years of treatment were so encouraging that in September 1935 we began to immunize a new

group of 24 children. The control Group B2 was made up of 14 patients who were studied for the two preceding years in control Group B1 and 20 new patients. By the end of the first year two children had drifted away and hence observations on only 32 control patients are presented here.

In Group A2 there were 11 males and 13 females. Their average age at the beginning of inoculations was 7.2 years. Five patients had severe heart disease. All the children in this group had a definite history of attacks of rheumatic fever.

During the course of treatment the average erythrocyte sedimentation rate and hemoglobin percentage were 7.8 mm. and 80 per cent respectively. The total number of colds was 103 for 20 children during two winters, or 4.2 per child. Four had chronic sinus infection during the first year and only two during the second. There were two attacks of rheumatic fever in two children. One of them was hospitalized for two months, although she showed no cardiac involvement and her white cell count and sedimentation rate were only slightly raised. The other case was diagnosed by a private physician and the boy stayed in bed at home for two weeks.

Indefinite subacute rheumatic symptoms were few in this group. Only four children showed frequent pallor (16.6 per cent), two children complained of abdominal symptoms on several occasions (8.3 per cent), four had frequent headaches (16.6 per cent) and only one had more than two nosebleeds (4.15 per cent). Not a single patient complained more than twice of transitory joint or muscle pains. There has been one admission to the hospital for rheumatic fever and one for pinworm infestation. Four children spent a month in the country. The average gain in weight per child was 10.9 pounds for two years. The five children who at the beginning of therapy were diagnosed as Class IIa cardiacs passed into Class I.

One child reported precordial pain on one occasion and another on two occasions. No other cardiac symptoms were recorded.

Group B2.—Thirty-two control patients were observed for the same period of two years. Their average age was 8.5 years. Fifteen were males and 17 females. Five belonged to cardiac Class II. The average hemoglobin percentage and sedimentation rate for this group were 76.8 and 10.7 mm. There were 130 upper respiratory infections reported by 23 patients and nine had chronic sinusitis throughout the time of observation. The usual treatment in the ear, nose, and throat department brought only transitory relief.

This group fared particularly badly as far as rheumatic fever was concerned. Fourteen patients had 17 attacks during the two consecutive winters. The disease in its acute manifestations affected 43.4 per cent of the entire group.

The subacute rheumatic symptoms were many and troublesome. Ten patients had chronic pallor (31.2 per cent), nine, or 28 per cent, fre-

quent attacks of vomiting and abdominal pain, 18, or 56 per cent, had constantly recurring headaches, many of them due in all probability to chronic sinusitis. Nine children (28 per cent) reported repeated nosebleeds, and 18, or 56 per cent, complained constantly of joint and muscle pains.

The cardiac symptoms were also prominent. Four children complained frequently of palpitation, seven of precordial pain, and ten of dyspnea. There were four hospital admissions for rheumatic fever, one for an appendectomy, two for otitis media, and seven patients received country care.

The average gain in weight however was good and almost identical with the treated group, namely 10.5 pounds.

Observations on Group A1 for Two Years Following Treatment

It was obviously of interest for us to know how the first treated group has fared since the inoculations were discontinued in June 1935. These patients have reported to the clinic regularly since then and it was easy to estimate their state of health.

Unfortunately one boy died of meningococcus meningitis at another hospital in May 1936. Previous to this he was in excellent health.

Of the other nine children one developed an attack of rheumatic fever with cardiac decompensation in March 1936 and was placed in cardiac Class IIa. He has been sent to a cardiac convalescent home. The remaining eight children have shown a perfect health record. Including the patient who had an attack of rheumatic fever, the average hemoglobin and sedimentation rate were 80 per cent and 9 mm. respectively. There was a total of 18 colds and no sinus infections. The total gain in weight was 150 pounds, or over 17 pounds per child. This record however is misleading, as one girl gained 41 pounds in two years from overeating. Her basal metabolism remained normal. In 1933 before the inoculations were begun, she was a Class IIb cardiac, in 1935 she was classed as IIa, and in 1937 as Class I, and then began to attend school for normal children. Another child passed from Class IIa to Class I.

Electrocardiographic Studies

It was of utmost importance to determine if the administration of hemolytic streptococcus filtrate had any adverse effect upon the myocardium, as might be revealed by a prolongation of the P-R interval or other changes. Electrocardiographic studies were made on each child in Group A2 just before the treatment was begun and at least twice during the course of treatment. No pathological changes were observed then. To determine whether the filtrate had any immediate deleterious effect upon the heart muscle, 20 out of 24 children had an electrocardiogram taken within twenty-four hours of the largest dose of the filtrate.

It will be seen from Table VII that only in one instance (Case 1) was the P-R interval prolonged from 0.19 second with a rate of 120 to 0.14 second at the rate of 150.

TABLE VII

COMPARISON OF P-R INTERVAL IN ELECTROCARDIOGRAMS OF 20 PATIENTS TAKEN BEFORE COMMENCEMENT OF TREATMENT AND WITHIN TWENTY-FOUR HOURS OF THE LARGEST DOSE OF THE HEMOLYTIC STREPTOCOCCUS FILTRATE

NO.	BEFORE TREATMENT		AFTER LAST INJECTION	
	RATE	P-R (SECOND)	RATE	P-R (SECOND)
1.	120-30	0.19	150	0.14
2.	100	0.18	90	0.17
3.	100	0.16	100	0.16
4.	100	0.16	74	0.16
5.	110-20	0.17	120	0.16
6.	100	0.18	100	0.18
7.	90	0.12	96	0.12
8.	96	0.19	110	0.18
9.	100	0.20	100	0.20
10.	110	0.16	110	0.16
11.	76	0.16	80	0.19
12.	100-90	0.20	90	0.20
13.	96	0.18	80	0.19
14.	90-80	0.18	80	0.19
15.	100-90	0.20	120	0.18
16.	90	0.16	86	0.16
17.	110-20	0.14	126	0.16
18.	80	0.20	90	0.20
19.	88	0.19	90	0.20
20.	110	0.16	120	0.12

COMMENT

From the above data it appears that the 34 children who have received inoculations of hemolytic streptococcus filtrate fared remarkably well as compared with the untreated groups and even with the average health experience of any group of normal children. Whether this was due to therapy or merely to a fortunate chance selection of patients cannot be stated dogmatically. We realize that the groups are too small to make definitive conclusions possible, but we cannot help feeling impressed by the low incidence of rheumatic symptoms and attacks of rheumatic fever in the treated group. Out of 34 children only two, or 5.9 per cent, developed the disease in its acute phase during the course of therapy, while the control groups showed 15 per cent and 43.4 per cent respectively. The physical condition of the control patients remained mediocre, and complaints of pains, headaches, and fatigue were frequent.

The purpose of this article is not to draw conclusions, but to state our observations. It is our intention to treat a much larger group of patients during the next two years and make extensive electrocardiographic studies in order to determine the immediate and remote effects of the filtrate on the heart muscle.

EVALUATION OF RESULTS IN TREATMENT OF PERIPHERAL CIRCULATORY DISEASES*

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DURING the past fifteen years there has been a noticeable change in the attitude of the profession toward the prognosis in patients with peripheral vascular diseases. Up to about the year 1925, the prevailing opinion was that little could be done for sufferers from the organic arterial diseases, and that eventually amputation of the extremities was usually necessary. This generally hopeless attitude was a reaction to the poor results of treatment obtained prior to this period.

The last decade has witnessed an extraordinary development of new methods of treatment for patients with peripheral circulatory disorders. Table I presents an incomplete list of the methods proposed and practiced during this time. The growing interest in this subject

TABLE I
METHODS USED IN TREATMENT OF PERIPHERAL VASCULAR DISEASE

Physiotherapy measures	
Heat	
Hot baths	
Baking	
Thermo-regulated cradle	
Diathermy	
Short wave	
Whirlpool baths	
Buerger's exercises	
X-ray treatment over spine	
Suction-pressure apparatus (Pavaex)	
Intermittent venous hyperemia	
Injections	
Hypertonic sodium chloride	
Sodium citrate	
Typhoid vaccine	
Insulin-free pancreatic tissue extract	
Paravertebral injections of alcohol	
Subarachnoid injections of alcohol	
Sodium thiosulfate	
Drugs	
Theobromine	Papaverine
Acetylcholine	Alcohol
Mecholin	
Nitrites	Allantoin
Iodides	Thioglycerol
Operations	
Perivascular sympathectomy (Leriche)	
Ganglionectomy	
Arteriectomy	
Vein ligation	
Peripheral nerve section	

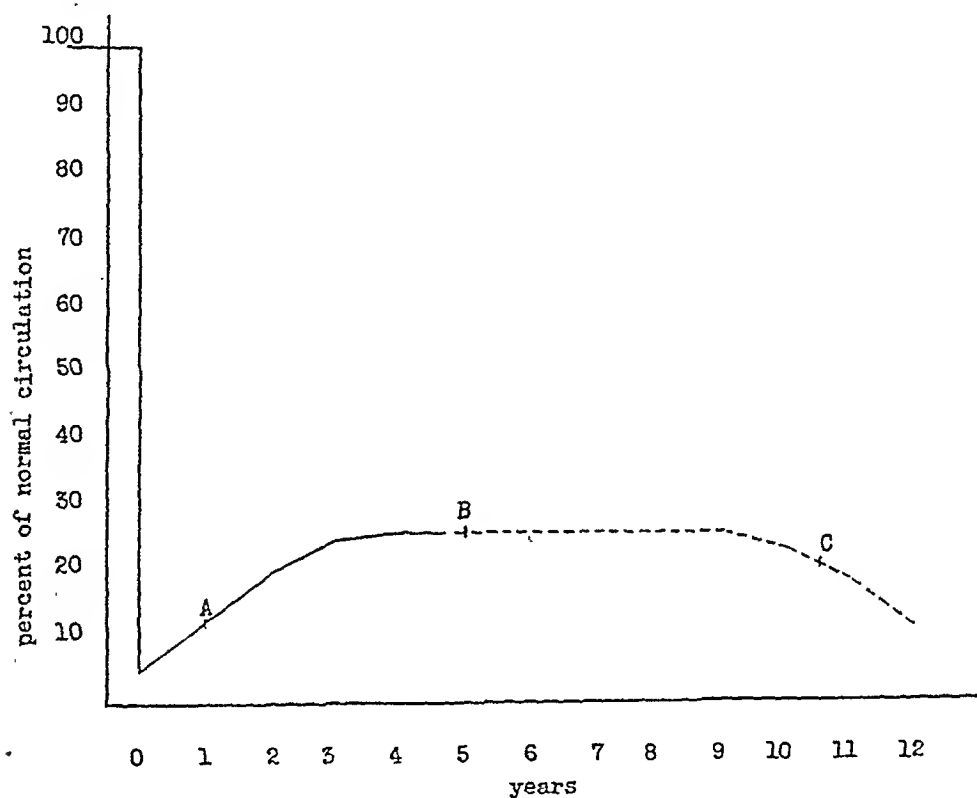
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has been reflected in numerous papers dealing with diseases of the peripheral circulation. Enthusiastic reports on the results of treatment by various methods have appeared, indicating a new spirit of optimism. In many of the reports of the good results obtained by different forms of therapy, a critical attitude is noticeably lacking. In numerous acute and chronic ailments it is the spontaneous course of the disease rather than the method of treatment which is responsible for the recovery of the patient. In the treatment of peripheral vascular disease there is too great a readiness to accept improvement as indicating the value of the treatment used. It is important to realize that in these conditions also considerable spontaneous improvement frequently takes place. Other factors, such as the benefit from cessation of smoking and the psychic effect of treatment, are frequently ignored.

Following occlusion of a major artery in an extremity, nature comes to the aid of the patient and quickly develops a collateral circulation. This process of building up a collateral circulation proceeds rapidly during the first year and continues for at least two or three years longer. While treatment may accelerate this process, it will occur even though no treatment is employed.

Figure 1 illustrates diagrammatically the changes in circulation which take place after such a closure. The first period is one of improvement of circulation due to the spontaneous development of collateral circulation. This process continues for two or three years whether or not treatment is used. Following this first period, the circulation remains at a remarkably stationary level for an indeterminate number of years, indicated by the broken line. During this second period the collateral circulation is maintained. In patients with arteriosclerosis there follows a third period when the collateral circulation itself gradually becomes involved by the arteriosclerotic process, causing a progressive diminution in circulation. It is at once apparent that it makes a great difference whether the patient is at point *A*, *B*, or *C* when first seen. If it is claimed that the patient who is at *A* responded well to a form of treatment, it is logical to point out that this patient was improving spontaneously and treatment may have had no influence whatsoever. If it is stated that as a result of treatment of a patient at *B* there was no increase in circulation but that the patient was prevented from becoming any worse, it is proper to point out that this patient was in a stationary phase, and that the treatment may have had nothing to do with his remaining in this condition. If, on the other hand, it could be shown that the patient at *B* showed definite improvement in circulation, the evidence of the value of the treatment would be more convincing. Similarly if the downward course of the patient at *C* were interrupted and reversed, the value of the treatment would be demonstrated.

Table II presents an individual case which illustrates such spontaneous improvement. An occlusion took place in this patient's left calf in November, 1927. Previously the oscillometer reading at the left calf was 4. After the occlusion it dropped to $\frac{1}{4}$. He was treated from November, 1927, to June, 1928, during which time the oscillometer readings repeatedly taken showed a change from $\frac{1}{4}$ to $\frac{1}{2}$. At this time, for economic reasons, the patient stopped treatment. Repeated examinations in the four following years nevertheless showed a continued rise in oscillometer readings to $2\frac{1}{2}$. In contrast to the recovery that took place in the left calf the oscillometer readings in the



development of
collateral
circulation

maintenance of
collateral
circulation

involvement of
collateral
circulation

Fig. 1.—Spontaneous improvement in circulation following sudden closure.

right calf in response to treatment, and during the years after treatments were stopped, remained at practically the same level. In the right calf the occlusion had taken place years before in 1924. The right leg was in a stationary phase and it remained in this phase throughout the period of observation.

It has been claimed that prevention of gangrene following occlusion of a major artery demonstrates the value of a method of treatment. If the tendency to spontaneous improvement is borne in mind, it is readily apparent that such evidence in the individual case is of little value. In a recent report from the Mayo Clinic on 100 patients who had had acute occlusion and who had received little treatment of any

kind, it was stated that 50 per cent failed to develop any gangrene.¹ A similar case is the following. A patient, fifty years of age, developed a coronary thrombosis. He remained in bed for four weeks and then began to walk around. Two weeks later the right lower extremity suddenly became numb and cold, obviously due to an embolism in the right femoral artery. Since this patient was of rather stolid type and apparently did not have very severe pain, he did nothing about it for four weeks. I first examined him at this time, and it was evident that the circulation in the major vessels of the right lower extremity had been almost completely occluded four weeks before. The oseillometer readings at the calf and ankle were 0. In spite of this serious impairment of circulation no gangrene had supervened. If this patient had been treated following the acute closure by the suction-pressure apparatus or any other form of treatment, it would no doubt have been claimed that the treatment was responsible for the preservation of the extremity. As a matter of fact spontaneous recovery was sufficient to avoid gangrene.

TABLE II
OSCILLOMETER READINGS ILLUSTRATING SPONTANEOUS IMPROVEMENT

ACUTE CLOSURE IN NOVEMBER, 1927 LEFT CALF		ACUTE CLOSURE IN 1924 RIGHT CALF	
October, 1927	4		1
November, 1927	$\frac{1}{2}$		1
December, 1927	$\frac{1}{2}$		1
February, 1928	$\frac{1}{2}$	Period of treatment	1
May, 1928	$\frac{1}{2}$		1
June, 1928	$\frac{1}{2}$		1
August, 1928	$\frac{1}{2}$		$\frac{1}{2}$
June, 1929	1 $\frac{1}{2}$		$\frac{1}{2}$
March, 1930	2	No treatment	$\frac{1}{2}$
February, 1931	2 $\frac{1}{2}$		1

A third form of improvement which is often cited as demonstrating the value of treatment is the healing of ulcers. Anyone who has had considerable experience in dealing with cases of peripheral vascular disease, soon learns that most ulcers tend to heal spontaneously. In an occasional case in which an ulcer has been present for years, and has shown no tendency to heal in spite of rest in bed, satisfactory healing under a method of treatment is impressive evidence of the value of such treatment. In general, however, one should be cautious in accepting such evidence.

These various phases of spontaneous improvement must be borne in mind and evaluated before conceding that a method of therapy has demonstrated value in the treatment of peripheral vascular disease.

The rôle of tobacco in the question of improvement must also be evaluated. It is well known that the smoking of two or three cigarets

results in marked vasoconstriction of the peripheral vessels.^{2, 3, 4} This has been shown both by plethysmographic and by skin temperature studies.^{2, 3, 4}

Figure 2 shows vasoconstriction after smoking, by a determination of the temperature of the fingers. During the smoking of two cigarettes the temperature of the fingers fell from 32° C. to 26° C., a drop of 6 degrees. After cessation of smoking there was a gradual return to a normal temperature. This effect of smoking is present in individuals with normal circulation as well as those with peripheral vascular disease. The constant use of tobacco undoubtedly maintains the vessels in a greater degree of vasoconstriction than would be normal. There may be other ways in which the constant use of tobacco affects ad-

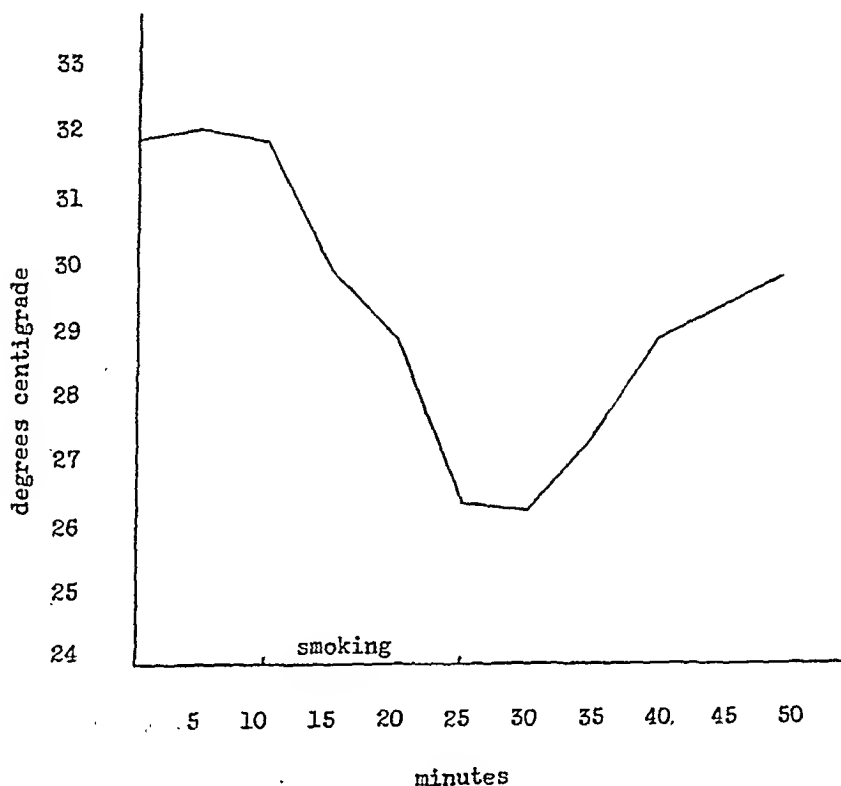


Fig. 2.—Fall in temperature of fingertips while smoking two cigarettes.

versely the circulation in the extremities. Clinical experience has amply demonstrated that the cessation of the use of tobacco in itself results in a definite improvement of circulation. In 20 instances of thrombo-angiitis obliterans in my experience where the disease was in a relatively early stage, cessation of smoking without any other form of therapy resulted in improvement or disappearance of all symptoms.

Table III shows the changes in such a case. The patient was a physician forty years of age suffering from intermittent claudication. He had an oscillometer reading of $1\frac{1}{2}$ at the ankle of the affected leg, which still indicated a fair circulation. I felt that active treatment was not necessary and advised merely cessation of smoking. A grad-

ual increase will be noted in oscillometer readings at the ankle from April, 1929, to May, 1930. Associated with this increase there was complete disappearance of symptoms. In May, 1930, apparently not convinced of the relationship between the use of tobacco and his symptoms, this patient resumed smoking. When seen in November the oscillometer reading had been reduced to 1 and there had been a return of symptoms. The patient again stopped smoking at this time and has not used tobacco since. He has now been followed up to May, 1937. The gradual improvement in circulation is evident. This patient is now entirely symptom-free and is engaged in an active practice which requires considerable activity. He had no treatment whatsoever.

Many similar instances could be cited. It is, therefore, apparent that if a patient is induced to stop smoking at the same time that a method of treatment is begun, the improvement that results may be entirely due to cessation of the use of tobacco and not at all to the treatment. In order to be certain that the cessation of the use of tobacco plays no rôle in improvement, smoking must have been stopped at least six months before treatment was started.

TABLE III
OSCILLOMETER READINGS ILLUSTRATING IMPROVEMENT AFTER CESSATION OF
SMOKING WITHOUT OTHER TREATMENT

LEFT ANKLE	
April, 1929	12
October, 1929	2½
May, 1930	3
	Resumed smoking
November, 1930	1
	Stopped smoking
February, 1931	2½
June, 1931	3
December, 1931	3
June, 1932	3
January, 1933	3
April, 1933	3
April, 1934	3½
April, 1935	3½
May, 1936	3½
May, 1937	4½

Finally it is necessary to consider the relationship of vasoconstriction to this question of evaluation of treatment. Until recent years there were no satisfactory objective methods of measuring circulation in the legs. Two methods that have been developed are now in general use. One of these is measurement by means of the oscillometer, and the second, measurement of skin temperature by means of electric thermometers. Increases in oscillometer readings and in the temperature of the toes are now frequently cited as objective evidence that the method of treatment employed has increased the circulation

in the extremities. While such objective evidence is valuable and convincing, there are certain errors in interpretation that must be avoided.

Regulation of the body temperature is a vitally important function. It is an extraordinary fact that changes in environmental temperature of as much as 50° F. are promptly compensated for by the regulatory mechanisms of the body so that the internal temperature remains unchanged at 98.6° F. One of the most important of these mechanisms is the regulation of the amount of blood flow in the extremities by means of vasoconstriction. To conserve heat when the environmental temperature is low the peripheral vessels are constricted to reduce the flow of blood. To increase heat elimination these vessels are dilated. The surface temperature at the tips of the extremities is usually much less than the forehead temperature, and the difference may be as much as 15° Centigrade.

Changes in the size of the peripheral vessels due to vasoconstriction are reflected in both oscillometer measurements and surface tempera-




	COLD ROOM 20°C (68°F)	NORMAL ROOM 27°C (80°F)	HOT ROOM 38°C (100°F)
SIZE			
OSCILLOMETER READING	3.0	4.5	6.0
TEMPERATURE OF GREAT TOE	20°C	26°C	34°C

Fig. 3.—Physiologic variations in normal blood vessels.

ture readings. Thus in a cold room with the vessels constricted the oscillometer reading at the ankle which is normally between 4 and 5 may be reduced to 3 or less (Fig. 3). In a hot room the reading may be as much as 6. Similarly the surface temperature of the great toe may be 20° C. in a cold room and 34° C. in a hot room. It is obvious that these fluctuations in oscillometer measurements and surface temperature readings do not indicate any disease in the blood vessels. They are normal variations which are characteristic of all healthy human beings.

The degree of vasoconstriction in peripheral vessels is similarly influenced by the mental state of the patient. Increased nervousness or emotional disturbance is likely to produce constriction, while mental relaxation will reduce this tendency. Such changes, also, are characteristic of all normal people.

Since the function of body heat regulation by means of vasoconstriction is so vitally important for good health, it is not surprising

that nature does not relinquish it when there is disease of the peripheral arteries. Even with advanced organic disease of the peripheral vessels there is still some superimposed vasoconstriction reducing the amount of blood flow to the extremity. It is only in the last stages of peripheral vascular disease, when the integrity of the extremity is actually threatened by loss of blood supply, that nature reluctantly gives up this ability to vary the volume of peripheral circulation.

Figure 4 illustrates a vessel whose lumen has been encroached upon by organic disease. When vasodilatation is produced in such a vessel by environmental changes the lumen is increased in size and more blood can flow through it.

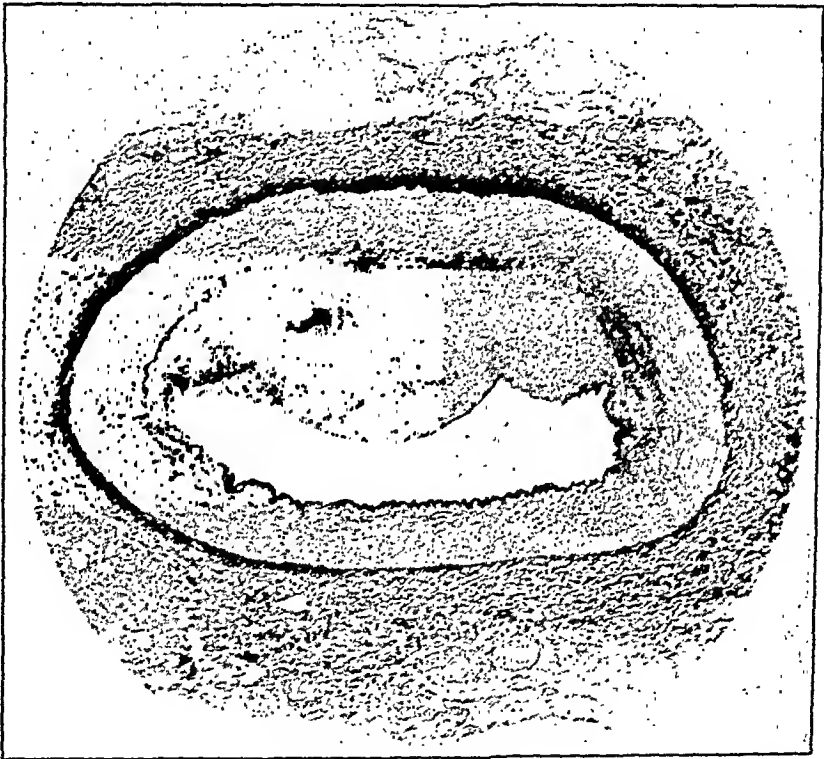


Fig. 4.—Cross-section of vessel showing encroachment of lumen by disease process.

Such alterations in the size of this diseased vessel will be reflected in variations of oseillometer measurements and surface temperature readings. These changes are diagrammatically represented in Fig. 5. When increased oseillometer measurements and surface temperature readings are offered as objective evidence of improvement in circulation, one must be sure that they are not normal variations due to differences in environmental temperature or in the patient's mental state.

How then is one to avoid this difficulty? There are two factors responsible for the reduction in blood flow. One is the actual reduction of the lumen of the blood vessels by organic disease. The second is the superimposed vasoconstriction. If all vasoconstriction could be abolished temporarily, the reduction in blood flow would then be due

only to the organic disease present. Measurements with the oscillometer and the skin thermometer under such conditions would reveal the real degree of improvement resulting from treatment.

There are many methods of temporarily eliminating vasoconstriction. For example any form of anesthesia accomplishes this purpose.



	BEFORE ANESTHESIA	AFTER ANESTHESIA
SIZE		
OSCILLOMETER READING	1.0	2.0
TEMPERATURE OF GREAT TOE	25°	30°

Fig. 5.—Diagram to illustrate changes in size of lumen of diseased vessel.

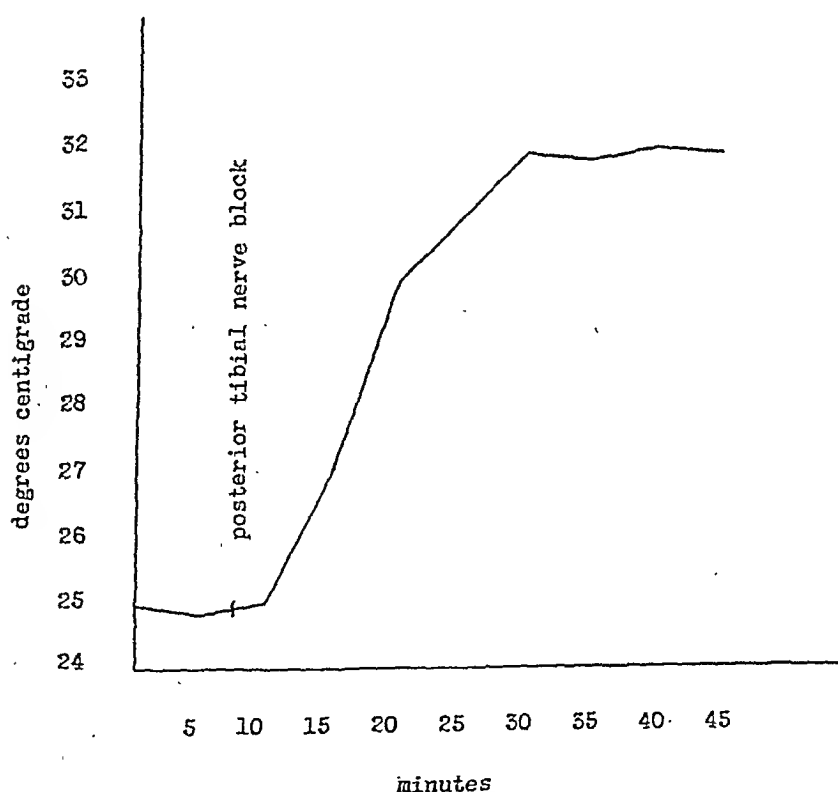


Fig. 6.—Changes in temperature of great toe following release of vasoconstriction by means of anesthesia.

General or spinal anesthesia may be employed, paravertebral injections of novocaine, or novocaine injections of the peripheral nerves. It has been found by experience that no matter which form of anesthesia is used, relatively complete vasodilatation is produced.⁵ For practical purposes in clinic or office practice, the simplest form of anesthesia is most suitable.

This is accomplished by a novocaine injection of the posterior tibial nerve at the ankle. This procedure releases vasoconstriction in the vessels of the foot. The increased blood flow causes an elevation of temperature which attains its maximum in about fifteen or twenty minutes (Fig. 6). The oseillometer measurement taken at the ankle reflects the maximum dilatation possible in the diseased vessels. The maximum temperature of the great toe and the maximum oseillometer measurements obtained under such conditions are objective measurements of the circulation when the vasoconstrictor factor is completely eliminated. A comparison can be made under similar conditions six months later, and if at that time increased readings can be demonstrated, the evidence of improvement is convincing. Table IV illustrates comparative readings made in this manner.

TABLE IV
COMPARATIVE MEASUREMENTS OF CIRCULATION BEFORE AND AFTER TREATMENT

	BEFORE ANESTHESIA	AFTER ANESTHESIA
	Before Treatment	
Oscillometer reading	1.0	1.5
Temperature of toe	25	29.5
	After Treatment	
Oscillometer reading	1.5	2.5
Temperature of toe	25	31.5

All of the cases coming for treatment to a large circulatory clinic are not suitable for evaluating the results of treatment. From among them, however, certain patients can be selected who may serve this purpose. The ideal case is an individual who has had intermittent claudication for at least two or three years so that the phase of spontaneous improvement has passed; one who has stopped smoking for more than a year; and perhaps one who has been treated for a considerable period by some method without improvement. This will rule out any psychic factor due to contact with the physician and will show that spontaneous improvement is not taking place. The circulation in such a patient should be studied by means of oseillometer readings and temperature studies after complete vasodilatation has been produced under anesthesia. He is now ready to be treated. If during the next year he shows steady subjective improvement and this improvement is supported by objective evidences, such as increased oseillometer and temperature readings under controlled conditions, we may permit ourselves to accept such evidence as indicating the value of the treatment.

SUMMARY

During the past decade a great variety of methods of treatment have been proposed to improve the circulation in individuals with peripheral vascular disease. Critical evaluation of these methods requires that

certain factors be determined. These are the tendency to spontaneous improvement after arterial occlusion, the effect of cessation of smoking and the normal variations in vasoconstriction due to environmental changes in temperature and in the patient's psychic state. Evidence of improvement can be accepted as indicating the value of a form of treatment only if it is shown that these factors have been eliminated.

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PAROXYSMAL BUNDLE-BRANCH BLOCK ASSOCIATED WITH HEART DISEASE

A REVIEW AND AN ANALYSIS OF THE LITERATURE, WITH THIRTEEN NEW
CASES AND NOTES UPON THE INFLUENCE OF THE VAGUS*

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THE increasing number of cases of transient or recurrent bundle-branch block which have been reported during the past few years indicates that this condition is not an uncommon one. Many of these cases have been classified as essentially functional, a term which in many instances is misleading. From a study of the literature and from our own material it is evident that a clear differentiation is important between the group associated with organic heart disease and the group described by Wolff, Parkinson, and White⁵⁷ with apparently congenitally wide QRS waves and short P-R intervals. In the latter, the delay in intraventricular conduction is of no serious significance. In the former the periods of bundle-branch block are primarily due to abnormal changes in the conducting tissue and are to be considered a manifestation of advanced heart disease. In some cases of this group certain physiological factors, particularly changes in vagal tone, may indirectly influence intraventricular conduction and be immediately responsible for the appearance or disappearance of branch block. In such cases, however, it is not justifiable to conclude that the vagal action is primarily or wholly responsible for the fluctuations in intraventricular conduction.

That type of bundle-branch block which is associated with very short P-R intervals has been thoroughly defined and well investigated and will be described only briefly in this report. The cases to be reported are confined to the group associated with organic heart disease with the possible exception of one case (Case 1). There are thirteen examples of this type of intermittent or transient bundle-branch block which have come to our attention during the past few years. In five cases we have recorded the transition from one degree of conduction to another. Observations directed toward studying the effect of changes in vagal tone in causing transitions to or from bundle-branch block were made in six cases.

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Cases With Wide QRS Waves and Short P-R Intervals

This group belongs to the type of bundle-branch block studied and described by Wolff, Parkinson, and White in 1930.⁵⁷ They presented a syndrome which is characterized by a distinctive electrocardiographic pattern, consisting of wide QRS complexes with short P-R intervals, occurring usually in young persons without other evidence of heart disease who are prone to attacks of paroxysmal auricular tachycardia, flutter, or fibrillation. There may be a reversion to the normal form spontaneously, during the paroxysmal tachycardia, after exercise or after the administration of atropine or quinidine. Holzmänn and Scherf²³ in 1932 and Wolferth and Wood⁵⁶ in 1933 have published critical studies of this condition and have independently suggested a very plausible explanation of its mechanism. They believe that the abnormal ventricular complex does not represent a block in a bundle branch but that it is due to the early arrival of an auricular impulse in one ventricle by way of a short-circuiting conducting bundle, such as a bundle of Kent. Although this is the probable mechanism, the electrocardiographic abnormality is still commonly classified as bundle-branch block and it will be so termed in this report. Some of these cases have now been followed for a number of years without manifestation of heart disease and consequently this condition is best considered at the present time simply as an unusual variation of the normal cardiac mechanism.

There should also be included among the inconsequential cases those rare individuals with no apparent cardiovascular disease in whom a bundle-branch block manifests itself after a prolonged period of paroxysmal tachycardia. This is interpreted as indicating fatigue of one of the bundle branches by the prolonged rapid rate. It has been pointed out, however, that this is most likely to occur in individuals in whom there is heart disease, so that such a finding should probably always be regarded with some suspicion.

TYPE ASSOCIATED WITH HEART DISEASE

In selecting cases from the literature, as with our own cases, we have limited ourselves to the classical form of bundle-branch block with Q-S intervals of 0.12 second or over, except for a few instances in which the intraventricular conduction time was over 0.10 but under 0.12 second. In the latter a marked change to or from a bundle-branch block shape of QRS complex in association with the prolongation of intraventricular conduction seemed sufficient to warrant their being interpreted as branch block. We have not included cases in which there has been only a slight change in the intraventricular conduction time or in which only isolated complexes showed bundle-branch block. Throughout this report the nomenclature proposed by Wilson and his coworkers^{4, 55} will be employed to indicate the bundle branch which is affected.

CASES

Cases 1 to 8 have been observed by us. Cases 9, 10, 11, and 12 were taken from hospital records. Case 13 was seen in private practice by an associate.* In the following cases the pulse and heart rates have been measured in beats per minute, the blood pressure in millimeters of mercury systolic and diastolic, and the Q-S and P-R intervals in seconds, and will be recorded simply numerically in the reports.

CASE 1.—A. S., female, aged forty-one years, entered the Boston City Hospital on June 21, 1935, and was discharged on August 31, 1935.

She complained of the progressive development of severe pain and swelling of her ankles for four days. For the preceding five weeks she had had vague migratory joint pains. There had been no recent infection and there were no cardiovascular symptoms. The past history was negative for rheumatic fever, arthritis and chorea.

Examination showed a patient who, although not acutely ill, was in obvious pain. The temperature was 100.2° F. and the pulse rate was 108. A soft, localized, apical, systolic murmur was the only abnormal physical finding in the heart. X-ray films of the heart showed it to be normal in size and shape. The blood pressure was 110/70. Both feet and ankles were swollen and exquisitely tender on motion. With the exception of a few carious teeth no other abnormalities were found.

Laboratory Data.—Repeated urine examinations, red and white blood cell counts, and hemoglobin determinations were normal. The corrected sedimentation rate (Ernstene method) showed the high value of 1.2 mm. per minute when done a few days after admission. Periodic determinations showed a gradual fall to 0.40 mm. per minute during the course of the following eight weeks. The blood Kahn reaction was negative for syphilis. Cervical smears revealed no gonococci and the gonococcal complement fixation test was reported as doubtful. The ankle joints were normal by x-ray.

Course.—She became clinically well after a few days. The temperature and joint pains subsided under sodium salicylate therapy. The systolic murmur disappeared and there was no clinical evidence of heart disease. The patient was followed regularly through 1936 and remained well, with no definite signs or symptoms of heart disease.

Electrocardiograms.—(Fig. 1.) During the eight weeks in the hospital eight routine electrocardiograms were taken and all but two showed right bundle-branch block (Q-S 0.12-0.14, P-R 0.16-0.18). The normal records (Q-S 0.07-0.08, P-R 0.18-0.20) appeared in the fourth and sixth weeks. Records showing right bundle-branch block were also obtained in September and October, 1935, and April, November, and December, 1936. The cardiac rate during branch block varied between 60 and 125, while during normal conduction the rates were 70 and 71. All records showed rather low amplitude of the QRS complexes but there were no T-wave changes in the records showing normal conduction.

Diagnosis.—Acute rheumatic fever.

Observations.—Observations were made on August 13, 14, 15, 16, and 30, 1935. Bundle-branch block was present when each of the following procedures was applied. No opportunity was presented for studying their effects on normal conduction because the observed normal periods were too short.

*For permission to include Cases 8 and 9, Case 10, Case 11, and Case 12, we are indebted respectively to Dr. Cadis Phipps, and Dr. J. A. Foley of the Boston City Hospital, and Dr. Ashton Grabel and Dr. H. B. Sprague of the Massachusetts General Hospital. For an electrocardiogram in Case 7 we thank Dr. C. R. Comstock of Saratoga Springs, N. Y.

Carotid Sinus Pressure: On August 13 transitions to normal were associated with carotid sinus pressure on five out of nine trials. On all of these occasions the transitions to normal conduction accompanied a reduction in heart rate and with reversion to a higher rate bundle-branch block reappeared. These transitions were usually associated with gradual alterations in heart rate although the changes in conduction took place suddenly without intermediate complexes. During the periods of normal conduction the heart rate varied between 75 and 85 while during bundle-branch block it ranged from 79 to 94. The rates below 85 with bundle-branch block occurred in those cycles just prior to transitions to normal conduction. On the occasions when no transitions occurred with carotid sinus pressure the minimum rate recorded was 85.

The effects of carotid sinus pressure were tested sixteen times in the course of the subsequent observations in August. No transitions to normal conduction occurred in spite of slowing of the rate which in two records on August 31 reached 49 and 54.

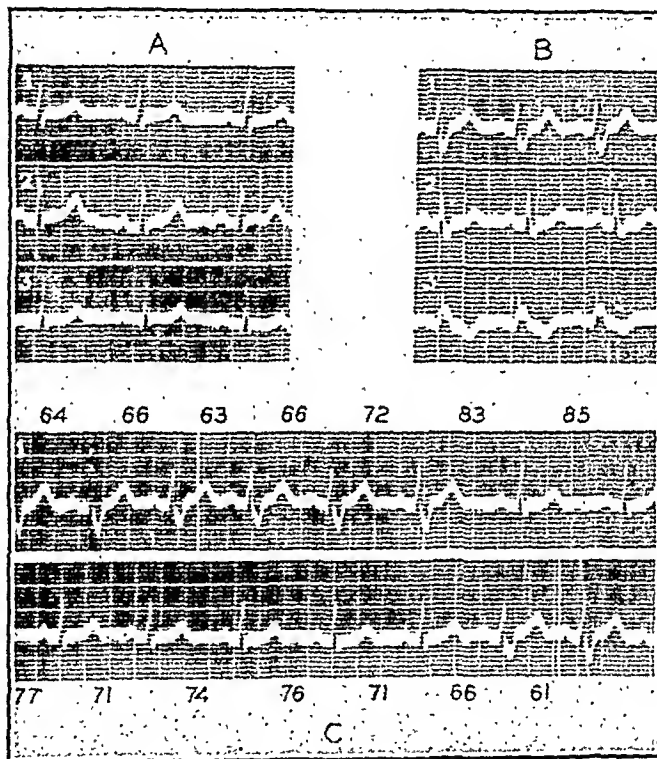


Fig. 1.—Case 1. A, (Aug. 5, 1935) normal conduction. B, (Sept. 27, 1935) right bundle-branch block. C, (Aug. 13, 1935) continuous record showing transition from right bundle-branch block to normal conduction produced by bilateral carotid sinus pressure (duration indicated by the vertical white signal lines) and return to branch block with release of pressure. Numbers refer to the R-R intervals and are in 0.01 sec. Time-marker 0.20 and 0.04 sec.

This slowing was the maximum obtained at any time. In the other fourteen trials the minimum heart rate was 85. Although slowing occurred, similar negative results were obtained in December, 1936.

Oculocardiac Reflex: This was tested on August 13 and 15. On the thirteenth the rate slowed from 94 to 75, with a change to normal complexes appearing when the rate was 79. On the fifteenth there was slowing from 100 to 85 without a transition.

Posture: On changing the position from sitting to reclining or vice versa transitions were recorded on two of six trials. On August 15, bundle-branch block was present at a rate of 85 in the sitting position and normal conduction at a rate of 75 in the reclining position. On August 16, normal conduction was present in both positions at a rate varying from 72 to 85 except for one period of six branch

block complexes (rate 75 to 79) which appeared and disappeared while the patient was sitting. On August 14 and 30, branch block was present in both positions with a minimum rate of 79.

Effect of Mild Exercise: This was tested on August 13 and 14. No records were taken prior to exercise. On the former date the rate slowed from 94 to 88 without improvement in conduction. On the latter the rate slowed from 88 to 79, normal conduction being present when the rate was 85 or less.

Nitroglycerine: Nitroglycerine, 0.65 mg., was administered in the usual manner. No alteration from branch block took place and the rate reached 130.

Atropine: Atropine sulfate, 1.0 mg., was injected intravenously. The heart rate rose to 135 and bundle-branch block persisted throughout.

Spontaneous Transition: On August 14 normal conduction (rate 85 to 88) was present throughout a control strip lasting 17.7 seconds, except for one period of six branch block complexes at a rate of 88.

Comment.—Although it is difficult to draw general conclusions from these observations the factor of cardiac rate seems to be an important one. Except for two short runs of bundle-branch block, normal conduction was always associated with a slower cardiac rate than the preceding or succeeding periods of block. This was particularly well shown on August 13 when transitions occurred at an apparently critical heart rate of about 85. The evidence indicates that the cardiac rate during the observations was a major factor in determining the presence or absence of bundle-branch block in the early period of the patient's course. The fact that it became progressively more difficult to influence the block during the latter part of August 1935 and the fact that normal conduction never appeared subsequently, either spontaneously or when every attempt was made to induce it a year later, strongly suggest that an organic factor was present which eventually caused permanent block to be established.

That the block was not the result of direct vagal influences was demonstrated by the inability of atropine to abolish it. It is quite probable that the increased heart rate which followed the administration of nitroglycerine may have offset any effect which coronary dilation might have had in improving the conduction.

Although we cannot definitely determine the nature of the organic changes which progressively damaged the right bundle branch we are tempted to attribute it to pathological changes incidental to a rheumatic infection. It is possible that rheumatic involvement of the small coronary twig supplying the right bundle branch may have resulted in gradual occlusion and ultimate fibrosis of the branch.* However, there is sufficient reason to warrant caution in definitely classifying the etiology of the branch block as rheumatic since there were no other manifesta-

*Yater has recently reported, at the annual scientific meeting of the American Heart Association (June 8, 1937), six new cases of bundle-branch block studied carefully post mortem by serial sections. Two of these patients had chronic rheumatic heart disease and their electrocardiograms had shown right bundle-branch block. In both, Yater found complete interruption of the right bundle branch with less damage to the left. He suggested that rheumatic involvement of the branches of the coronary artery supplying the conducting tissue may have been the pathological process in these cases.

tions of rheumatic carditis and since it is known incidentally that delayed A-V conduction in acute rheumatic fever usually disappears. At present, however, the rheumatic etiology seems more likely than any other.

CASE 2.—C. McD., female, aged thirty-eight years, entered the Boston City Hospital for the first time Jan. 3, 1936, and was discharged April 16, 1936.

She had been active and well until three months before admission, at which time dyspnea on exertion gradually appeared and became progressively worse. Edema of the feet and ankles had appeared a month before entry. There was no previous history of rheumatic infection.

Examination showed a slightly enlarged heart with a regular rhythm and a rough but faint apical systolic murmur. X-ray cardiac measurements were: to the right of the median line 3.4 cm., to the left 9.9 cm., internal diameter of the thorax 25.0 cm. and great blood vessels 5.5 cm. The blood pressure was 105/65. The lungs were clear. The liver edge was 3 cm. below the costal margin and there was moderate pitting edema up to the knees and in the sacral region. No other abnormalities were observed.

Laboratory Data.—Urine and blood examinations were negative on admission but the leucocyte count rose after ten days in the hospital and remained between 10,000 and 14,000 per cu. mm. until discharge. The corrected sedimentation rate (Ernstene method) fluctuated between 2.90 and 0.70 mm. per minute. The Kahn test on the blood was negative for syphilis. Total serum proteins were 6.2 gm. per cent, with an albumin-globulin ratio of 1.0. Blood cultures showed no growth.

Course.—The patient was digitalized and given routine cardiac treatment. There was temperature up to 100° F. in the evenings and a pulse rate between 90 and 100 for two weeks. She was then given acetylsalicylic acid and the temperature and pulse rate promptly subsided. Symptomatically she improved gradually but she was kept in the hospital for a number of weeks because there was evidence of active infection.

The patient was readmitted on Oct. 16, 1936, and was discharged on Feb. 20, 1937.

Since her previous admission she had remained fairly well except for slight dyspnea on exertion until one month before readmission when she began to experience dull nonradiating substernal pain unrelated to food or exertion. This pain came during night or day and lasted about an hour. The dyspnea on exertion became worse, palpitation was more marked, and edema of the ankles returned.

Examination revealed essentially the same signs in regard to the cardiovascular system except that a slight bulge was noted on fluoroscopy in the region of the left auricle which was interpreted as a rheumatic deformity. Some dullness, diminished breath sounds, and moist râles were found at the right lung base. A varying amount of edema was present during her stay in the hospital.

Laboratory Data.—Urine and blood examinations were negative except for the leucocyte count which varied between 5,000 and 13,500. The corrected sedimentation rate was 0.68 mm. per minute on admission and thereafter fluctuated between 0.40 and 1.30 mm. per minute. The serum proteins were normal.

Course.—For a time she improved, but periodic low fever persisted, and dyspnea and edema recurred when she was allowed up. On Feb. 1, 1937, her tonsils were removed and bilateral tonsillar abscesses drained. Following this operation there was a distinct but gradual improvement and she was discharged nineteen days later, fever, dyspnea, and edema having disappeared.

Electrocardiograms.—(Fig. 2.) From January to April, 1936, nine routine electrocardiograms were taken. The first two, taken on January 9 and 16, showed left bundle-branch block (Q-S 0.12-0.14, P-R 0.20). The remaining seven showed

normal conduction (Q-S 0.07-0.08, P-R 0.16-0.20). During the second admission ten routine records were taken. The first, on October 17, showed left bundle-branch block (Q-S 0.12-0.14, P-R 0.16). On December 14 there was delayed A-V conduction (Q-S 0.08, P-R 0.23) and on February 10, 1937, intraventricular conduction was slightly prolonged (Q-S 0.10-0.11). The remaining seven records taken at intervals throughout her course showed normal conduction (Q-S 0.07-0.08, P-R 0.16-0.20). The records showing normal intraventricular conduction also showed left axis deviation and diphasic or inverted T-waves in Lead I, attributed to digitalis. In neither admission was there a constant correlation between the cardiac rate and the form of the electrocardiogram.

Diagnosis.—Myocarditis, ? rheumatic.

Observations.—On October 19 an observation was made on the influence of respiration. Three transitions from normal conduction (Q-S 0.06, P-R 0.14) to left bundle-branch block (Q-S 0.10-0.12, P-R 0.14-0.16) occurred spontaneously during

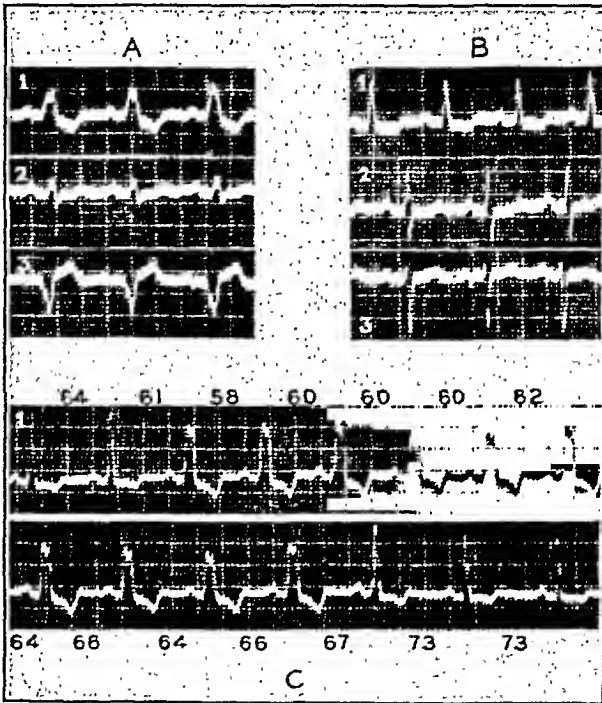


Fig. 2.—Case 2. A, (Jan. 9, 1936) left bundle-branch block. B, (Feb. 8, 1936) normal condition. C, (Oct. 20, 1936) continuous record showing spontaneous appearance and disappearance of left bundle-branch block during quiet respiration in the sitting position. Numbers refer to the R-R intervals and are in 0.01 sec. Time-marker 0.20 and 0.04 sec.

quiet respiration in the recumbent position. Deep sustained inspiration and expiration did not change normal conduction to branch block. On October 20 no periods of branch block were observed during quiet respiration, inspiration, expiration, or carotid sinus pressure with the patient recumbent. In the sitting position, however, periods of left bundle-branch block (Q-S 0.11-0.12, P-R 0.14) were recorded on nine occasions, the longest lasting eighteen seconds. Although the effects of the procedures mentioned above were tested, these periods of defective conduction all occurred during quiet respiration either before or after some procedure was carried out. On October 21 one short period of bundle-branch block (9 complexes) was recorded during quiet respiration in the recumbent position. In the sitting position, however, during quiet respiration consecutive records by the three standard leads covering fifty-nine seconds showed branch block throughout.

It was an invariable finding during these observations that when bundle-branch block was present the heart rate was greater than during normal intraventricular conduction. The periods of branch block showed rates varying from 86 to 104 while the rates during normal conduction varied between 62 and 95. The average difference in rate between periods of defective conduction and the preceding or succeeding periods of normal conduction was 10 beats per minute, with extremes of 4 and 16. The changes in rate were gradual and occasional transitional complexes were seen. It should be noted that here, as in Case 1, although there was an association between the cardiac rate and the form of the electrocardiogram at the time of these observations, no such association existed from day to day as manifested in the routine tracings.

Comment.—In each admission left bundle-branch block was recorded during the early period when the clinical evidence of poor myocardial function was most marked. With improvement the branch block disappeared. Consequently we feel that the tendency toward block was dependent primarily upon the state of the myocardium and that the cardiac rate, at times, was the immediate factor determining the absence or presence of defective conduction. The natural tendency for the heart rate to increase when a person rises to the sitting position may account for the fact that transitions to branch block occurred more frequently in this position.

CASE 3.—M. R., negress, aged fifty-one years, was admitted to the Boston City Hospital April 14, 1936, and was discharged May 30, 1936.

She complained of having had slowly increasing dyspnea on exertion for five years and of swelling of the ankles for one year. During the four months prior to admission she had become much worse, with dyspnea at rest and attacks of paroxysmal nocturnal dyspnea. There was no substernal pain. She had known of arterial hypertension for three years before entry.

Examination revealed great dyspnea and slight cyanosis. There was marked narrowing of the retinal arteries and the peripheral arteries were thickened and tortuous. The heart was enlarged, the apex impulse being in the fifth intercostal space 3 cm. beyond the midclavicular line. X-ray cardiac measurements were: to the right of the median line 6.0 cm., to the left 11.0 cm., internal diameter of the thorax 25.0 cm., and great blood vessels 8.0 cm. The heart showed general enlargement. The rhythm was regular, but the heart sounds were of poor quality. There was a protodiastolic gallop rhythm and a high pitched blowing apical systolic murmur. The blood pressure was 168/140. Numerous moist râles were heard at the lung bases. The liver edge was not felt and there was no dependent edema.

Laboratory Data.—The urine showed an occasional trace of albumin. The urine concentration test showed a minimum specific gravity of 1.008 and a maximum of 1.012. The phenolsulphonephthalein test showed an excretion of 55 per cent of the dye in two hours. The blood nonprotein nitrogen varied between 26 and 30 mg. per cent. The total blood serum protein was 5.1 gm. per cent.

Course.—With routine cardiac therapy the patient made a slow recovery but her convalescence was interrupted by bronchopneumonia. The blood pressure fell to 140/100. She was followed after her discharge and when last seen on April 15, 1937, she complained of substernal oppression, dyspnea on exertion, palpitation, and nervousness. There was no edema. Her blood pressure was 204/130.

Electrocardiograms.—(Fig. 3A.) During her hospital stay six routine records were taken. On May 7 and 27 there was normal conduction (Q-S 0.10, P-R 0.16-

0.18) with rates of 68 and 70 respectively. The records on April 15, May 14, 19, and 20 showed left bundle-branch block (Q-S 0.16, P-R 0.18) with rates varying from 67 to 85. During eleven months following discharge eight records were obtained. In June, July, and November, 1936, and January and April, 1937, left bundle-branch block (Q-S 0.14-0.16, P-R 0.14-0.16) was present with rates varying from 85 to 105. In August, 1936, and February and March, 1937, there was normal conduction (Q-S 0.10, P-R 0.16) with rates of 78 to 81. When normal conduction was present the records showed left axis deviation with inverted T-waves in Lead I and low upright or inverted T-waves in Lead II.

Diagnosis.—Hypertensive heart disease with left ventricular failure. Bronchopneumonia.

Observations.—On May 19, 0.3 c.c. of amyl nitrite was inhaled. The heart rate rose from 109 to 124. No alteration to normal conduction took place. On May 25 normal intraventricular conduction was present throughout in spite of deep sustained inspiration and expiration. On Jan. 7, 1937, when bundle branch block was present the application of right and left carotid sinus pressure did not alter either the heart rate or the conduction time. When normal conduction was present on February 4 carotid sinus pressure again failed to influence either the rate or the conduction and sustained inspiration and expiration were likewise ineffective. Climbing one flight of stairs raised the rate from 77 to 108 but normal conduction remained.

Comment.—No correlation was found between the clinical state of the patient and the presence or absence of branch block. It is possible that the cardiac rate played some rôle in determining the degree of intraventricular conduction, but the T-wave changes strongly suggest that coronary artery disease affecting the left bundle branch was the major factor in this patient.

CASE 4.—P. D., male, aged fifty-six years, was admitted to the Boston City Hospital for the first time May 27, 1936, and was discharged June 4, 1936.

He complained of weakness of the right side of the face and inability to speak both of sudden onset and of one day's duration.

Examination revealed a right facial paralysis of the central type and a motor aphasia. The heart was enlarged. X-ray cardiac measurements were: to the right of the median line 4.5 cm., to the left 10.0 cm., internal diameter of the thorax 29.0 cm. and great blood vessels 6.5 cm. The rhythm was normal but there was a loud rough apical systolic murmur. The blood pressure was 220/118. There were many moist râles at both lung bases. No dependent edema was present.

Laboratory Data.—The urine contained a trace of albumin and the blood nonprotein nitrogen was 28 mg. per cent. Blood cell counts were normal. The blood Hinton reaction was negative for syphilis.

Course.—The patient improved gradually and was discharged with a slight residual paralysis and moderately slurred speech. The blood pressure on discharge was 185/110.

He was readmitted to the hospital Oct. 4, 1936, and was discharged Oct. 17, 1936.

At this time he complained of increasing dyspnea and fatigue for three weeks. He had had several attacks of paroxysmal nocturnal dyspnea during this period. A recent respiratory infection had increased his symptoms.

Examination revealed essentially the same clinical and x-ray findings as before. There was still a residual right facial weakness and slurred speech. The blood pressure was 235/120.

Laboratory Data.—Urine and blood were essentially normal. The phenolsulphone-phthalein test showed 65 per cent excretion of the dye in two hours. The urine concentration test gave a minimum specific gravity of 1.008 and a maximum of 1.011.

Course.—He was digitalized and with routine cardiac care he improved rapidly. The blood pressure on discharge was 185/95. He was seen again in January, 1937. He had considerably restricted his mode of living and as a result he had few cardiovascular symptoms. At this time slight apical systolic and faint aortic diastolic murmurs were found. The blood pressure was 180/76.

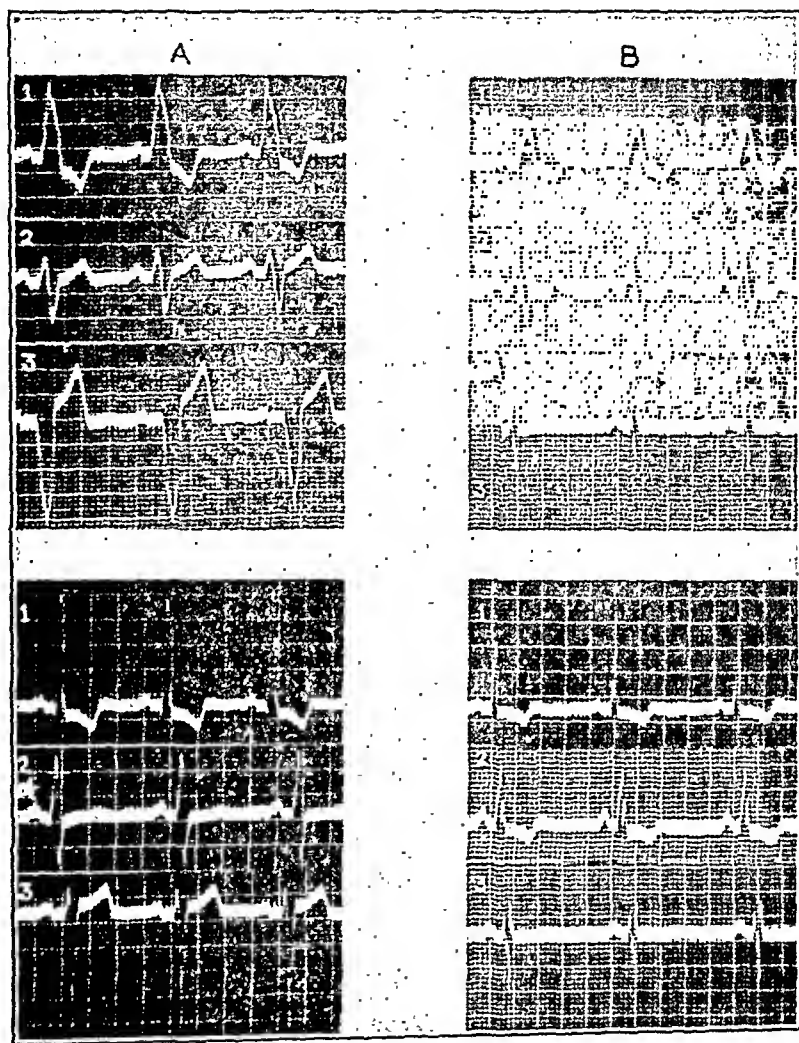


Fig. 3.—A, Case 3, upper, (May 20, 1936) left bundle-branch block. Lower, (May 27, 1936) normal conduction.
B, Case 4, upper, (Oct. 6, 1936) left bundle-branch block in Leads I and II, normal conduction in Lead III.
Lower, (Oct. 8, 1936) normal conduction. Time-marker 0.20 and 0.04 sec.

Electrocardiograms.—(Fig. 3B.) The only record taken during his first admission showed normal conduction (Q-S 0.10, P-R 0.14) with a rate of 70. Two days after readmission the first routine record showed left bundle-branch block (Q-S 0.16, P-R 0.16) in Leads I and II, with a rate of 67, while Lead III showed normal conduction (Q-S 0.08, P-R 0.16), with a rate of 62. Three more routine records at this time and two taken in January, 1937, all showed normal conduction (Q-S 0.08-0.10, P-R 0.16-0.20) at rates varying from 60 to 75. In all records the T-waves in Leads I and II were diphasic or inverted and usually were of low origin. Left axis deviation was present.

Diagnosis.—Hypertensive and coronary heart disease with slight aortic regurgitation. Left ventricular failure. Cerebral thrombosis.

Observations.—On October 9 sustained inspiration and expiration, as well as changing the posture from lying to sitting, did not alter normal conduction. Right carotid sinus pressure with the patient recumbent induced sinus standstill and an idioventricular rhythm at a rate of 35. The same procedure in the sitting position induced sino-auricular bradycardia (rate 48). Left carotid sinus pressure in both positions induced complete A-V dissociation (auricular rates 46 to 48, ventricular 40 to 48). No change to bundle-branch block occurred. On January 11, 1937, right and left carotid sinus pressure induced sinus standstill with an idioventricular rhythm (Q-S 0.08-0.10) at rates of 33 to 37.

Comment.—The only recorded episode of bundle-branch block in this patient occurred during a period of left ventricular failure and it is probably to be related to the temporary myocardial dysfunction and possibly to coronary artery disease. The block was probably intermittent during this period in spite of the fact that only one such episode was recorded.

CASE 5.—L. N., male, aged forty years, was admitted to the Boston City Hospital for the first time on Jan. 19, 1926, and was discharged Feb. 6, 1926.

He gave a previous history of severe acute rheumatism at the ages of fourteen and thirty-six years. Three weeks before entry he caught a "cold" and migratory joint pains developed four days before he came to the hospital. For five years he had noticed palpitation and some dyspnea on exertion but he had not been incapacitated by these symptoms.

Examination revealed a slightly enlarged heart, with the left border of dullness 10.5 cm. to the left of the midsternal line. The heart rhythm was regular and the rate was 65. A blowing apical systolic murmur and an early blowing diastolic murmur at the base were present. The blood pressure was 125/85. Moist râles were heard at the lung bases but engorgement of the cervical veins, palpable liver and edema were absent.

Laboratory Data.—The urine and blood examinations and Wassermann reaction were negative.

Course.—He was treated with sodium salicylate and his joint symptoms cleared rapidly.

He entered the hospital for the second time Dec. 19, 1932, and was discharged Jan. 24, 1933.

For two weeks prior to admission he had suffered from frequent "fainting spells." His cardiovascular symptoms had remained of mild degree.

Examination showed the heart to be of essentially the same size as before. The rhythm was regular. (Variations in cardiac rates are given with electrocardiograms.) A systolic thrill was felt in the aortic area and there were present characteristic aortic and mitral systolic and diastolic murmurs. The blood pressure was 122/70. There was no evidence of heart failure.

Course.—While in the hospital he had frequent syncopal attacks when no heart beats were heard. He was treated with ephedrine sulfate by mouth. These seizures ceased after two weeks.

At the age of fifty years he was admitted for the third time Dec. 30, 1936, and was discharged Jan. 7, 1937.

He had been followed since his previous discharge and in 1934 his pulse had become permanently slowed at a rate of approximately 35. He had, however, experienced

no syncope attacks until the day of his admission when he had two while in bed. Slight dyspnea on exertion had persisted but there were no other cardiovascular symptoms.

Examination showed no essential changes from the findings recorded above except for a heart rate of 38 and a blood pressure of 135/70. X-ray cardiac measurements were: to the right of the median line 6.0 cm., to the left 11.0 cm., internal diameter of the thorax 29.0 cm., and great blood vessels 5.5 cm. There was no evidence of heart failure.

Course.—He remained comfortable and had no syncope attacks. Ephedrine sulfate was given without appreciable change in heart rate.

He was admitted for the fourth time April 1, 1937, and he died April 6, 1937.

Sore throat and epistaxis developed three weeks before entry and were followed by hot painful swelling of the wrists. The joint pains and malaise persisted until admission. His cardiovascular symptoms had remained unchanged.

Examination showed large injected tonsils and mild cervical adenitis. The wrists were red, swollen, and tender. The cardiovascular findings were essentially the same as were present on the previous admission. The temperature was 101.6° F.

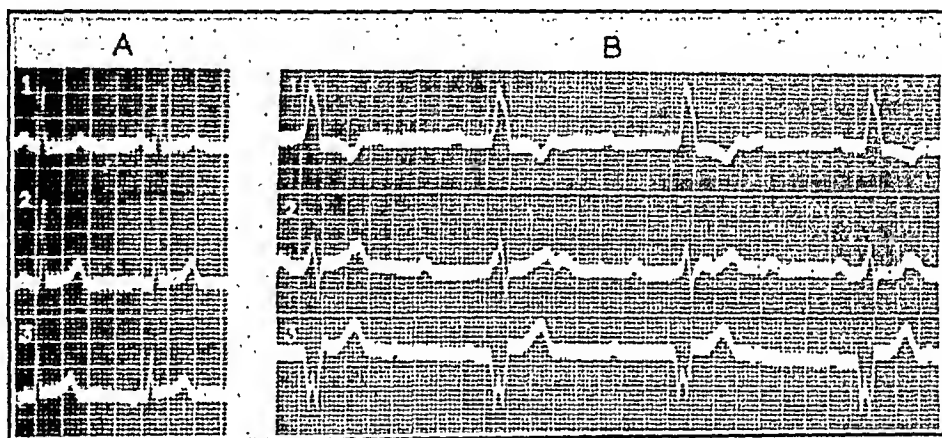


Fig. 4.—Case 5. *A*, (Jan. 21, 1933) normal conduction. *B*, (Jan. 5, 1937) left bundle-branch block and complete A-V dissociation. Time-marker 0.20 and 0.04 sec.

Laboratory Data.—The urine contained a small trace of albumin. The blood was normal.

Course.—He was given sodium salicylate and the fever disappeared in twenty-four hours. The heart rate on admission was 95, but on the evening of the second day he had three attacks characterized by convulsions and loss of consciousness. At this time the cardiac rate was found to be 28. He was given ephedrine and had no more attacks. He appeared to be improving but on the fifth day was found dead in bed.

Electrocardiograms.—(Fig. 4.) During his first admission two routine records showed normal sinus rhythm (Q-S 0.06, P-R 0.18-0.20) with rates of 60 to 67. In the early part of his second admission one record showed complete A-V dissociation with left bundle-branch block (Q-S 0.14), two showed complete A-V dissociation with a lesser degree of intraventricular block (Q-S 0.12-0.14) and one showed 2:1 A-V dissociation with left bundle-branch block (Q-S 0.16, P-R 0.20). The ventricular rate varied from 41 to 46. During the last four weeks of this hospital stay two records showed slight retardation of intraventricular conduction (Q-S 0.11-0.12) and four were normal (Q-S 0.06-0.10, P-R 0.14-0.20) the rate varying from 60 to 84. Two routine records were taken during the third admission. Both showed complete

A-V dissociation and left bundle-branch block (Q-S 0.16) with ventricular rates of 43 and 40. During his last stay in hospital three records were taken, all on April 2. At 10 A.M. there was complete A-V dissociation, the auricular rate being 110 and the ventricular 88, with right bundle-branch block (Q-S 0.14); at 4:30 P.M., after a syncopal seizure, complete A-V dissociation was still present with the same auricular rate but the ventricular rate had fallen to 24 and left bundle-branch block (Q-S 0.16) had reappeared; at 9:30 P.M. complete A-V dissociation was shown and the ventricular complexes were those of left bundle-branch block, but minor variations in the shape of the ventricular complexes at this time indicated a varying site of origin in the junctional tissue. The auricular and ventricular rates were 130 and 26 respectively. No axis deviation or T-wave changes were noted in the normal records.

Autopsy.—The heart weighed 710 gm. The right ventricle was markedly dilated and its wall measured 0.4 cm. in thickness. The left ventricular wall was 2.0 to 2.5 cm. in thickness but the cavity was not dilated. The tricuspid and pulmonary valves were normal. The mitral valve, 6.8 cm. in circumference, was greatly narrowed, the leaflets were thickened, and the chordae tendinae were shortened and thickened. The aortic valve, 6.1 cm. in circumference, showed marked interadherence of the cusps which were thickened, retracted, and fixed. There was no evidence of acute endocarditis. The openings of the coronary arteries were unaffected and the vessels showed minimal atherosclerosis. Apart from chronic passive congestion of the liver, spleen, and kidneys and atelectasis of the lower parts of both lungs there were no other gross pathological findings. Microscopic examination of the heart showed dense fibrous scarring of the aortic ring, the membranous part of the septum, and the upper part of the muscular portion of the septum under the left ventricular endocardium. In addition, throughout the heart, including the upper part of the septum, there were many areas of intense infiltration with lymphocytes, plasma cells, and fibroblasts mostly perivascular in position. There were distinct Aschoff nodules to be seen. The conduction system was not studied.

Diagnosis.—Acute rheumatic fever. Acute and chronic rheumatic heart disease with aortic and mitral stenosis and regurgitation.

Observations.—On January 5, 1937, right and left carotid sinus pressure and forced inspiration and expiration against closed air passages, all in both the sitting and recumbent positions, and the inhalation of 0.17 c.c. of amyl nitrite failed to influence the ventricular rate or intraventricular conduction.

Comment.—In 1933 there was transient, and in 1937 persistent, complete A-V dissociation and left bundle-branch block, the pathological basis for which is to be found in the wide-spread fibrosis in the region of the aortic ring and the upper part of the interventricular septum. The appearance a few days before death of a rapid ventricular rate in the presence of the complete A-V dissociation with complexes of right-branch block form may be attributed to the irritation of a lower impulse center by the acute rheumatic process. This center was probably situated below the lesion in the left branch and thus produced complexes of right branch block type. When the irritation disappeared the former and slower center above the level of the branch block again dominated the ventricles and the left bundle-branch block reappeared. An alternate explanation suggested by Yater⁵⁰ is that there was damage to both bundle branches, more advanced on the left, with the usual pacemaker being situated in

the right branch below the lesion on that side. However, for the reasons given above, it is probable that the pacemaker in this case shifted for a short time to the left branch below its lesion and right bundle-branch complexes ensued.

CASE 6.—J. H., male, aged fifty-seven years, was admitted to the Massachusetts General Hospital April 6, 1937, and was discharged April 27, 1937.

He had been perfectly well until three weeks before entry when he began to feel tight, low substernal pain when walking, which disappeared immediately with rest. Two days before admission while at rest he had one attack of pain which radiated down both arms. At 2:30 A.M. on the morning of entry he was awakened by a con-

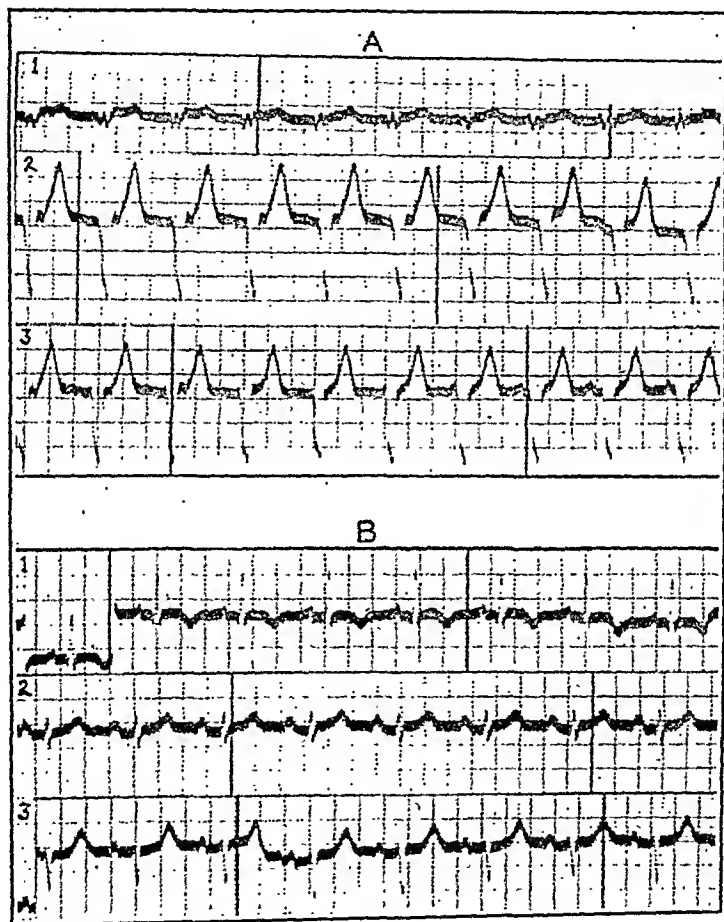


Fig. 5.—Case 6. A, (April 6, 1937) left bundle-branch block and complete A-V dissociation. B, (April 7, 1937) normal conduction. Time-marker 0.2 and 0.1 sec.

stant, severe, substernal pain which gradually disappeared during the course of the following fifteen hours. There were no other symptoms except some belching of gas and sweating.

Examination eight hours after the onset of pain revealed a man who did not appear particularly ill. The cardiac apex impulse was felt in the fifth intercostal space 9 cm. from the midsternum. The cardiac rhythm was regular and there were no murmurs, pericardial friction, or gallop rhythm. The blood pressure was 142/100. No signs of heart failure were present.

Laboratory Data.—The blood leucocyte count was 14,000 per cubic millimeter on admission. The urine was normal. The blood Wassermann and Hinton reactions were negative for syphilis.

Course.—The temperature on admission was 101° F. During the course of the next five days this gradually fell to a normal level. The blood pressure established itself at a level of 130/80. He was kept in bed and given aminophyllin. His convalescence was uneventful.

Electrocardiograms.—(Fig. 5.) Eight electrocardiograms were taken during the hospital stay. The first, taken eight hours after the onset of pain, showed left bundle-branch block (Q-S 0.13) with what was apparently complete A-V dissociation with a rapid ventricular rate. The auricular and ventricular rates were both 100. On the following day and in the subsequent records the A-V and intraventricular conduction were normal (Q-S 0.07-0.08, P-R 0.20). There was moderate to marked left axis deviation in all records showing normal conduction. The Q-wave in Lead IV was absent in all records and there were progressive changes in the T-waves of Leads I, II, and IV in the last seven records indicating a recent myocardial infarct.

Diagnosis.—Coronary heart disease. Acute coronary thrombosis (anterior type).

Comment.—There can be little doubt that the conduction disturbances observed in this patient were due to either direct or indirect effects of

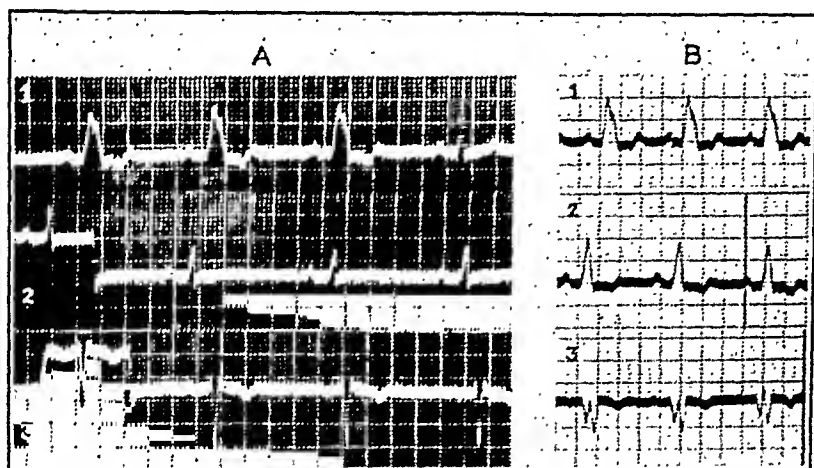


Fig. 6.—Case 7. A, (September, 1936) Lead I spontaneous transition from left bundle-branch block to normal conduction; Leads II and III, normal conduction. Time-marker 0.20 and 0.04 sec. B, (March 16, 1937) left bundle-branch block. Time-marker 0.2 and 0.1 sec.

a myocardial infarct involving the bundle of His. Temporary interference with the local circulation or involvement of the conduction system by the less irrevocable changes occurring at the periphery of the infarcted area can explain their transient nature.

CASE 7.—T. A., female, aged fifty-four years, was first seen in private consultation at the Massachusetts General Hospital in August, 1936.

At that time she complained that she was awakened at night by severe attacks of substernal pain which radiated into the left arm. For the previous six months she had noticed a tight substernal feeling when walking which occasionally radiated down the left arm. This would subside after five or ten minutes of rest. All of these symptoms had recently been considerably relieved by nitroglycerine and aminophyllin. Arterial hypertension of 170/110 had been discovered on routine examination in 1931.

Examination revealed an enlarged heart. The orthodiagraphic measurements were: transverse diameter of the heart 12.0 cm., internal diameter of the thorax

21.8 cm. The rhythm was regular. The aortic second sound was accentuated and there was a slight basal systolic murmur. The blood pressure was 150/100. No other abnormalities were found.

Electrocardiograms.—(Fig. 6.) Four electrocardiograms were taken. Left bundle-branch block (Q-S 0.16, P-R 0.19) was present in June and August, 1936. In September, 1936, the electrocardiogram showed a transition from branch block (Q-S 0.16, P-R 0.19) to normal complexes (Q-S 0.08, P-R 0.19) in Lead I. The normal type persisted through Leads II and III. The cardiac rate during block ranged from 63 to 59 while during normal conduction the rate varied from 52 to 56. A record taken on March 16, 1937, showed left branch block throughout (Q-S 0.17).

Diagnosis.—Hypertensive and coronary heart disease. Angina pectoris decubitus.

Comment.—Angina pectoris decubitus indicates considerable coronary insufficiency and it is probable that variability of a partially deficient blood supply to the conducting tissue was the primary factor determining the presence or absence of branch block.

CASE 8.—J. R., male, aged forty-one years, was first admitted to the Boston City Hospital Jan. 15, 1935, and was discharged Feb. 7, 1935.

He complained of increasing dyspnea on exertion for one year and of a vague dull precordial pain present when he was tired. No other cardiovascular symptoms were elicited.

Examination was negative except for a blood pressure of 160/110.

Laboratory Data.—Urine and blood were normal.

Course.—He improved with bed rest and symptomatic treatment. The blood pressure on discharge was 125/90.

He was admitted for the second time on June 18, 1936, and was discharged on June 28, 1936.

At this time he complained of increasing dyspnea on exertion for six months, orthopnea for three months and severe attacks of paroxysmal nocturnal dyspnea for one week.

Examination showed slight distension of the cervical veins and an enlarged heart. X-ray cardiac measurements were: to the right of the median line 7.0 cm., to the left 12.5 cm., internal diameter of the thorax 30.0 cm., and great blood vessels 9.5 cm. The rhythm was regular and there were no murmurs. The blood pressure was 140/100. A tender liver edge was felt 3 cm. below the costal margin. Moist râles were present at both lung bases. There was no peripheral edema.

Laboratory Data.—The urine and blood were normal.

Course.—He was digitalized and given diuretics. Under this regime improvement was rapid.

He entered the hospital for the third time July 25, 1936, and was discharged Sept. 15, 1936.

On the day of admission he had a fainting spell. He also complained of increased dyspnea, occasional precordial pain on exertion, and blurring of vision.

Examination revealed essentially the same findings as on his previous admission except that a moderate blowing systolic murmur was heard at the apex. The blood pressure was 138/108. Signs of pulmonary congestion were present but the liver was not felt and there was no peripheral edema.

Course.—While in the hospital he had several moderately severe attacks of paroxysmal nocturnal dyspnea which were relieved by morphia. His digitalis ration was increased, diuretics were administered, and he improved gradually. He was seen

again on January 15, 1937, when he complained of dyspnea on exertion. He exhibited a well-marked pulsus alternans and his blood pressure was 138/88.

Electrocardiograms.—(Fig. 7A.) All seven electrocardiograms taken between January, 1935, and August, 1936, showed left bundle-branch block (Q-S 0.14-0.16, P-R 0.16-0.18). Four subsequent records in September, 1936, and January, 1937, showed normal conduction (Q-S 0.08-0.10, P-R 0.16-0.18). During branch block the rate varied from 79 to 108 while during normal conduction it ranged between 79 and 97. The records showing normal conduction also showed left axis deviation and well-marked inversion of the T-waves in Leads I and II with low origin.

Diagnosis.—Hypertensive and coronary heart disease.

Observations.—On January 15, 1937, the effects of deep respiration, forced inspiration, and expiration against closed air passages and carotid sinus pressure were tested. The first two procedures had no effect on rate or conduction. Eight trials of carotid sinus pressure each resulted in S-A slowing without A-V block, the minimum rate recorded being 30. On two occasions when slowing was marked (40 and 30) a single broad complex of bundle-branch block type appeared (Q-S 0.16, P-R 0.18) but otherwise no change in conduction occurred. Climbing one flight of stairs induced dyspnea, raised the heart rate from 71 to 88, but did not alter the normal conduction.

Comment.—In this case there was no correlation between the form of the electrocardiogram and the clinical condition of the patient. The T-wave changes indicate coronary disease and the persistence of normal conduction since September 1936 may possibly be associated with the establishment of collateral circulation and better vascularization of the conducting tissue.

CASE 9.—B. B., female, aged forty-four years, was first admitted to the Boston City Hospital April 6, 1934, and was discharged April 14, 1934.

She complained of increasing dyspnea on exertion for six months. Arterial hypertension had been discovered during a pregnancy in 1928 and had been present since that time, with nervousness and headaches.

Examination showed the heart to be enlarged, with the apex impulse in the fifth intercostal space 12.5 cm. to the left of the midsternum. There was a soft basal systolic murmur. The blood pressure was 270/150. The lungs were clear and no edema was present.

Laboratory data.—The urine had a specific gravity of 1.015 to 1.017 and contained a trace of albumin. The blood nonprotein nitrogen was 34 mg. per cent.

Course.—After rest and sedation she was discharged improved, with a blood pressure of 180/120.

The patient was readmitted Sept. 10, 1935, and she died Nov. 30, 1935.

Because of increasing dyspnea she had been in and out of bed during the interval since discharge. For seven months she had had increasing edema of the lower extremities and frequent attacks of paroxysmal nocturnal dyspnea. She had taken three grains of digitalis daily for the preceding three months.

Examination revealed the cardiac apex to be in the midaxillary line. X-ray cardiac measurements were: to the right of the median line 7.2 cm., to the left 11.7 cm., internal diameter of the thorax 25.3 cm., and great blood vessels 6.5 cm. The rhythm was regular and no murmurs were present. The blood pressure was 270/170. Both lungs were dull on percussion and moist râles were present. Fluorocopy revealed a slight amount of pleural fluid bilaterally and hilus congestion. There was edema of the legs, abdominal wall, and back. A tender liver edge was felt 5 to 6 cm. below the costal margin.

Laboratory Data.—The urine examinations showed a small to large trace of albumin, with occasional granular casts. The concentration test showed a minimum specific gravity of 1.010 and a maximum of 1.014. The phenolsulphonephthalein test showed only 25 per cent excretion of the dye after two hours. The blood nonprotein nitrogen varied between 35 and 55 mg. per cent. There was a moderate normochromic anemia.

Course.—Under treatment with bed rest, digitalis, diuretics, and other routine cardiac measures the manifestations of heart failure gradually diminished during

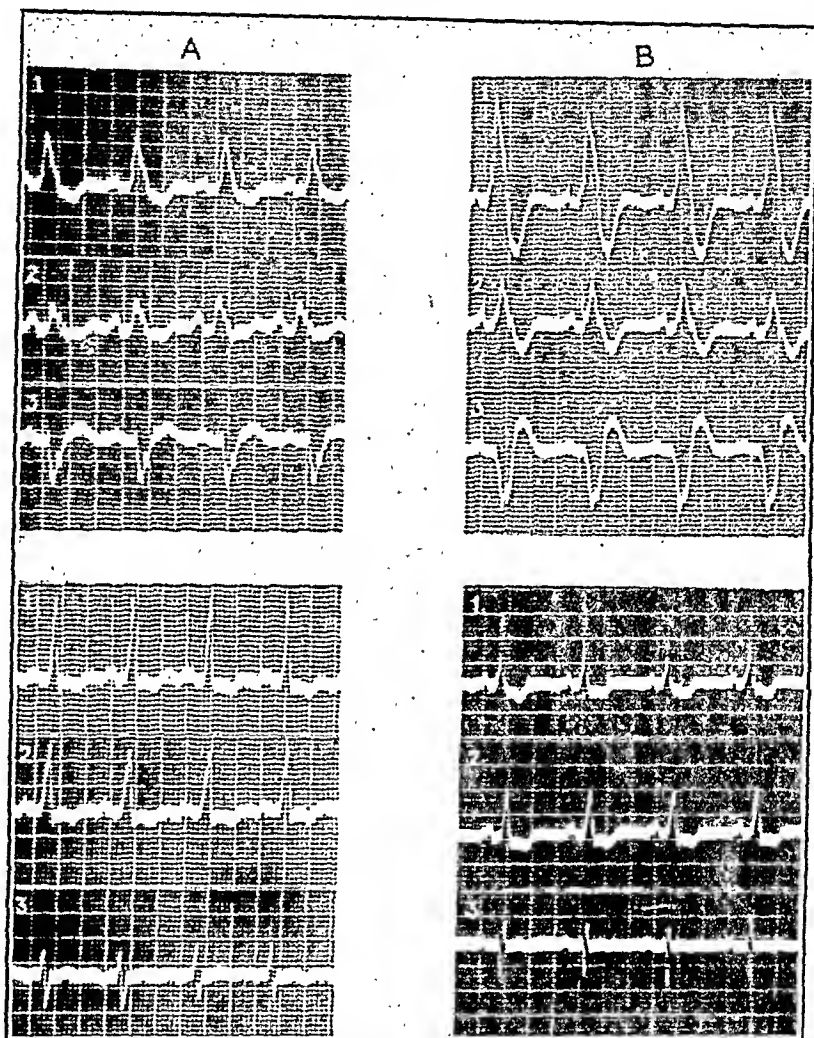


Fig. 7.—A, Case 8, upper, (June 19, 1936) left bundle-branch block. Lower, (Sept. 2, 1936) normal conduction.

B, Case 9, upper, (Sept. 11, 1935) left bundle-branch block. Lower, (Sept. 26, 1935) normal conduction. Time-marker 0.20 and 0.04 sec.

the first month. The blood pressure fell to 220/110. Edema, however, returned in the fifth week and ascites and pleural fluid gradually accumulated and persisted in spite of vigorous therapeutic measures. In the eighth week the temperature, previously normal, suddenly rose and signs of infection at the left lung base appeared. From this time onward she failed more rapidly and died in the tenth week.

Electrocardiograms.—(Fig. 7 B.) Eleven electrocardiograms were taken, of which six showed normal conduction (Q-S 0.09-0.10, P-R 0.12-0.16) with rates varying from 88 to 107, and five, including one record taken during the early part of the first admission, showed left bundle-branch block (Q-S 0.16-0.20, P-R 0.12-0.14) the rates ranging from 77 to 97. Of the normal electrocardiograms four occurred during the first month of the second admission when improvement was taking place. Left bundle-branch block was present on entry and again during the latter part of her

course when failure recurred. Normal conduction, however, was present on two occasions during this terminal period. There was no constant correlation between the form of the electrocardiogram and the cardiac rate in these routine records. Of the six records with normal conduction all showed inversion of the T-waves in Leads I and II with low origin. The electrical axis was normal.

Autopsy.—(Limited to the heart and kidneys.) The heart weighed 660 gm., with the left ventricle measuring 2.5 cm. in thickness and the right 0.8 cm. The coronary arteries were minimally affected, showing only slight yellow intimal thickening which caused no narrowing. Microscopic examination of the myocardium showed many small scattered fibrous scars with a slight amount of infiltration by polymorphonuclear cells and macrophages. In one section there was a fresh thrombus which almost completely occluded the lumen of an arteriole. The conduction system was not studied. The kidneys together weighed 200 gm. and were of the granular type with the cortex measuring 3 to 5 mm. Microscopic examination revealed many cortical scars with hyalinized glomeruli and atrophied tubules. There was arteriolar narrowing with thrombi in various stages of organization.

Diagnosis.—Hypertensive heart disease with failure. Vascular nephrosclerosis, possibly malignant.

Comment.—The bundle branches were not examined microscopically but it seems likely that the numerous small scars found scattered throughout the myocardium involved the region of the conducting tissue as well and partially damaged a bundle branch. The factor of myocardial failure seems to have been an important one but the fact that normal conduction was present in the latter part of her course indicates an additional factor which may have been circulatory in nature.

CASE 10.—M. S., female, aged forty-five years, was first admitted to the Boston City Hospital Oct. 1, 1936, and was discharged Nov. 12, 1936.

She gave a history of having spent four months in a hospital with rheumatic fever at the age of seven years. Since that time she had had no joint pains but had suffered from frequent sore throats and in recent years had noticed some dyspnea and palpitation on exertion. Six days before entry she had a chill and developed a cough. On the day previous to admission she developed pleuritic pain in the left chest and her ankles, elbows, and shoulders became painful. With the onset of the pulmonary infection increasing dyspnea rendered her unable to sleep.

Examination revealed a cyanotic patient who was markedly dyspneic, with a temperature of 102.5° F. and a respiratory rate of 40 per minute. The cervical veins were engorged. The entire precordium was heaving and the maximum apical impulse was felt in the anterior axillary line. There were a loud systolic murmur and a moderate mid-diastolic rumble at the apex. A basal systolic murmur was also present. The rhythm was regular. The blood pressure was 140/80. Dullness and moist râles were found at both lung bases extending on the left to the angle of the scapula. The abdomen was distended and there was tenderness in the right upper quadrant. Pitting edema was present in the lower extremities. The elbows, shoulders, and especially the ankles were tender.

Laboratory Data.—The urine contained a small trace of albumin. Blood examinations showed a mild normochromic anemia. On admission there was a polymorphonuclear leucocytosis with a count of 21,000 per cubic millimeter which gradually fell to normal. The blood Hinton reaction was negative for syphilis. Two blood cultures produced no growth.

Course.—The patient had a fluctuating fever for three weeks and thereafter with the diminution in the pulmonary signs the fever subsided and the dyspnea improved.

With digitalization the signs of cardiac failure gradually disappeared. The joint pains similarly cleared during the course of the first three weeks. Two weeks before leaving the hospital her pulse which had previously been regular became irregular.

She was readmitted Feb. 21, 1937, and she died March 30, 1937.

In the interval between admissions she was largely confined to bed, complaining of cough, orthopnea, and dyspnea. She was taking three grains of digitalis daily. Three weeks prior to readmission she developed pains in her feet, knees, hands, and elbows and ankle edema appeared.

Examination revealed cervical venous distension. The precordium was heaving with the maximum impulse in the anterior axillary line. X-ray cardiac measurements were: to the right of the median line 5.2 cm., to the left 11.0 cm., internal diameter of the thorax 25.0 cm., and great blood vessels 6.0 cm. Systolic and late diastolic murmurs were heard at the apex and a systolic murmur and a greatly accentuated pulmonary second sound at the base. The blood pressure was 160/65. Dullness and diminished breath sounds were found at both lung bases. There was

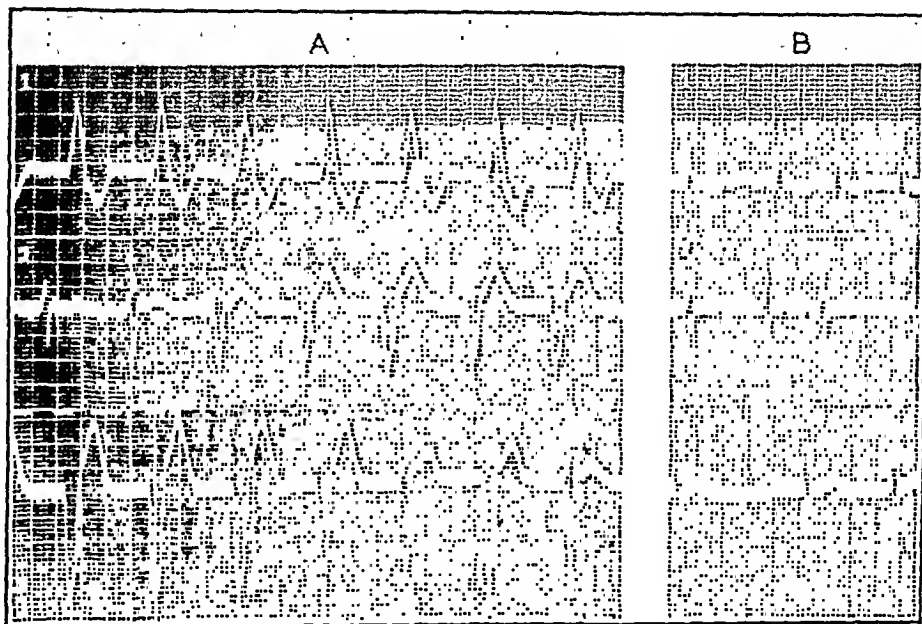


Fig. 8.—Case 10. A, (Oct. 5, 1936) auricular fibrillation and idioventricular rhythm. Lead I, left bundle-branch block; Lead II spontaneous transition from normal intraventricular conduction to left bundle-branch block; Lead III reverse transition. Note intermediate complexes. B, (Oct. 26, 1936) auricular fibrillation, normal intraventricular conduction. Time-marker 0.20 and 0.04 sec.

slight pitting edema of the ankles. There was stiffness and tenderness of the left ankle and the metacarpophalangeal joints on both sides. The temperature was 99.2° F.

Laboratory Data.—The urine contained a trace of albumin. The blood leucocyte count varied between 7,600 and 11,300 per cubic millimeter. There was a mild hypochromic anemia. The blood nonprotein nitrogen was 24 mg. per cent.

Course.—The slight fever subsided in three days. Local applications relieved the joint pains and with digitalis the cardiac symptoms improved except for occasional bouts of severe dyspnea. On March 20 her throat became sore and joint pains reappeared. She became febrile, cyanosed, and dyspneic. Hemolytic streptococci were grown from throat smears. The temperature rose to 107° F. and the pulse rate to 140 just before death ten days later.

Electrocardiograms.—(Fig. 8.) In the first admission six routine records were taken. On October 2 and 3 there was auricular fibrillation with a regular idio-

ventricular rhythm, the ventricular rates being 80 and 90 respectively and the Q-S intervals 0.08. On October 5 auricular fibrillation with a regular ventricular rhythm at a rate of 88 was still present, but there were, in addition, periods of left bundle-branch block (Q-S 0.14). Several intermediate complexes were recorded at this time. On October 6 the electrocardiogram showed auricular fibrillation and a regular ventricular rhythm at a rate of 81 with left bundle-branch block (Q-S 0.14) throughout. On October 26 and 27 there was auricular fibrillation but the complete irregularity of the ventricular rhythm (rates approximately 80 and 95) indicated resumption of A-V conduction. The intraventricular conduction was now normal (Q-S 0.08-0.10). In the second admission three records were taken. All showed auricular fibrillation and normal intraventricular conduction (Q-S 0.10). The record on Feb. 23, 1937, showed a regular idioventricular rhythm at a rate of 55, while those taken on February 25 and 26 showed an irregular ventricular rhythm at rates of 40 and 45 respectively. Left axis deviation was present in all records.

Autopsy.—The pericardial cavity was obliterated by fibrous adhesions. The heart weighed 530 gm. and showed hypertrophy of the right ventricular wall (thickness 0.8 cm.) and dilatation of the left auricle. The left ventricular wall measured 1.5 cm. in thickness and the cavity was not dilated. There was thickening of the leaflets and thickening and shortening of the chordae tendineae of the mitral valve (circumference 9.0 cm.). The other valves were unaffected. The myocardium showed no abnormality. There was slight atherosclerosis of the coronary arteries. The other gross pathological findings consisted of a chronic adhesive pleuritis on the right side, marked edema of both lungs, and ascites. Microscopic examination showed occasional Aschoff nodules in the myocardium.

Diagnosis.—Acute rheumatic fever. Chronic rheumatic heart disease with mitral stenosis and regurgitation. Congestive failure. Bronchopneumonia.

Comment.—During the first admission, although the patient had a recurrence of acute rheumatic fever, the conduction defects were present at the time when she was seriously ill with chronic rheumatic heart disease and cardiac failure, precipitated by pneumonia. Both the idioventricular rhythm and the bundle-branch block disappeared with clinical improvement. During the second admission although heart failure was present in varying degrees, bundle-branch block was not recorded, but no electrocardiograms were taken during the most severe period.

CASE 11.—H. W., male, aged sixty-five years, was admitted to the Massachusetts General Hospital Sept. 28, 1935, and discharged Nov. 13, 1935.

He had been in good health until the day before admission when he suddenly developed a severe precordial and substernal pain which was only partially relieved by a hypodermic injection of morphine. This pain continued with lessening intensity for the succeeding thirty-six hours. Other than slight dizziness and a desire to eructate there were no associated symptoms.

Examination revealed a moderately sick man, with slight cyanosis of the lips. The cervical veins were not engorged. The heart was slightly enlarged the left border of dullness being in the fifth intercostal space 10 cm. from the midsternal line. The cardiac rhythm was regular and the rate 65. The heart sounds were faint. No murmurs were present. The blood pressure was 120/78. There were a few moist râles at both lung bases but neither enlargement of the liver nor peripheral edema was present.

Course.—On admission the temperature was normal but the blood leucocyte count was elevated to 21,800. Treatment consisted of bed rest, aminophyllin, and symp-

tomatic therapy. In the second week there appeared at the left lung base increased moist râles with bronchial breathing and x-ray opacity. These signs were accompanied by a slight fever and a rise in the blood leucocyte count and were regarded as being due either to bronchopneumonia or to pulmonary infarction. He recovered rapidly from this pulmonary process and had an uneventful convalescence.

Electrocardiograms.—(Fig. 9.) Thirteen routine electrocardiograms were taken during the hospital period. Left bundle-branch block (Q-S 0.15-0.17) was present on September 30 and normal intraventricular conduction (Q-S 0.07-0.09) on the remaining twelve occasions. On September 28, 29, 30, and October 2 there was complete A-V dissociation (auricular rates 80 to 100, ventricular 50 to 65). This was followed on October 3 and 4 by delayed A-V conduction (P-R 0.29 and 0.25). The succeeding records showed normal conduction. Progressive changes from coved S-T segments to late inversion of the T-waves in Leads II and III were observed. In January, 1937, the T-waves in Leads II and III were low while the T-waves in Lead III still showed late inversion. There was moderate left axis deviation in all records.

Diagnosis.—Coronary heart disease. Acute coronary thrombosis (posterior type).

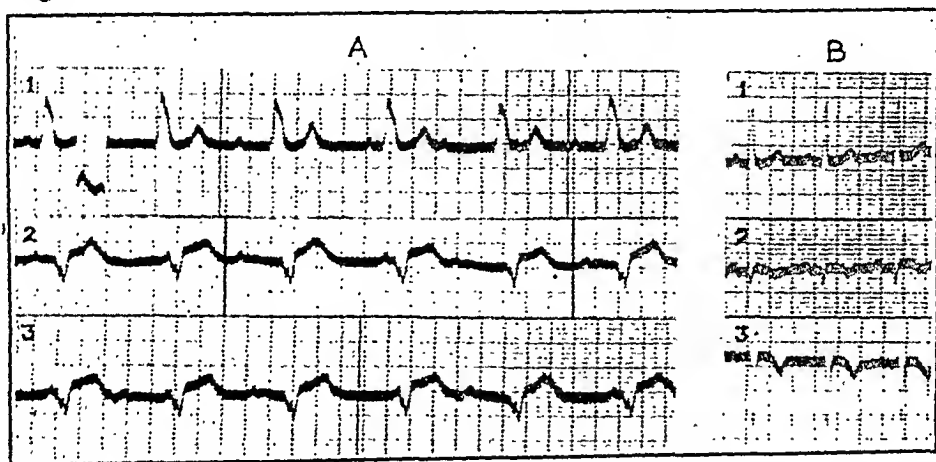


Fig. 9.—Case 11. A, (Sept. 30, 1935) left bundle-branch block and complete A-V dissociation. B, (Oct. 29, 1935) normal conduction. Time-marker 0.2 and 0.1 sec.

Comment.—In this instance, as with Case 6, the transient conduction disturbances can be correlated with the direct or indirect effects of an acute myocardial infarct.

CASE 12.—H. C., female, aged fifty-five years, came to the out-patient department of the Massachusetts General Hospital Dec. 27, 1935, complaining of dyspnea on exertion and of orthopnea.

Examination revealed a woman somewhat dyspneic at rest. The heart was enlarged with the left border of dullness 13 cm. from the midsternum. The cardiac rhythm was regular. The heart sounds were distant and there was a moderate blowing apical systolic murmur. The blood pressure was 200/100. The breath sounds at the left lung base were diminished and there were a few moist râles at both bases. A tender liver edge was felt 3 to 4 cm. below the costal margin. No edema was present.

Course.—On digitalis and bed rest the patient made considerable improvement during the following two weeks. Her blood pressure, however, remained high (230/130). She was not seen again until March 27, 1936, and at this time she was essentially in the same condition as when first seen. She had been overactive during

the interval and when advised to limit her activities she again improved and a month later there were no manifestations of myocardial failure except dyspnea on moderate exertion. Her blood pressure continued to be elevated. Attempts to follow her failed and she was not seen after May 22, 1936.

Electrocardiogram.—(Fig. 10.) A routine electrocardiogram taken on April 7, 1936, showed left bundle-branch block (Q-S 0.17, P-R 0.17) in Lead I while in Leads II and III there was normal conduction (Q-S 0.06-0.09, P-R 0.17). The cardiac rate was 86 throughout.

Diagnosis.—Hypertensive heart disease with failure.



Fig. 10.—Case 12. (April 7, 1936) Lead I, left bundle-branch block; Leads II, and III, normal conduction. Time-marker 0.2 and 0.1 sec.

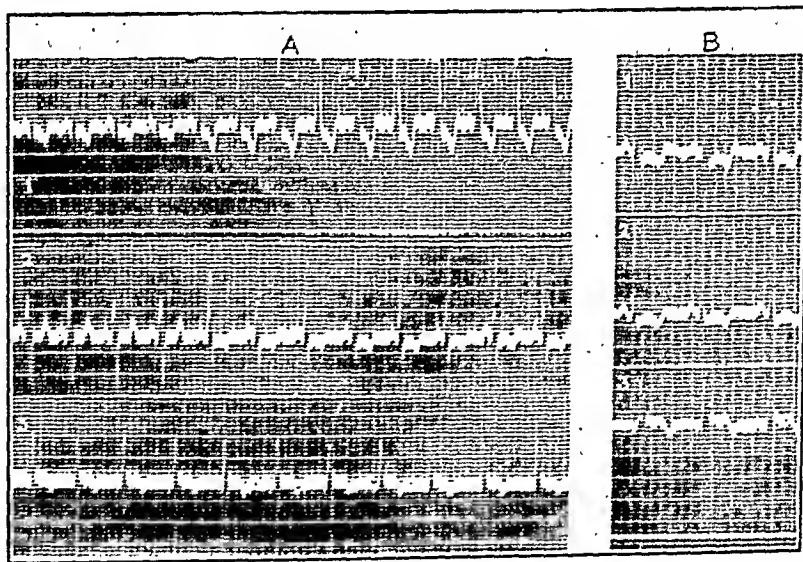


Fig. 11.—Case 13. A, (Nov. 12, 1929) Lead I, transition from normal conduction to left bundle-branch block; Lead II, reverse transition; Lead III, normal conduction. B, (Aug. 5, 1931) normal conduction. Time-marker 0.1 sec.

Comment.—The only electrocardiogram of this patient was taken during cardiac failure. As in Case 4 the branch block was probably intermittent during this time although only one period of block was recorded.

CASE 13.—E. K., female, aged seventy-three years, was first seen in private consultation Nov. 12, 1929, and was followed until death in October, 1931.

She complained of pains across the chest radiating down both arms occurring frequently on exposure to cold or on walking. The pain was relieved by rest. There were no other cardiovascular symptoms.

Examination showed the heart to be slightly enlarged, with the apex impulse in the fifth intercostal space 3 cm. to the left of the midclavicular line. There was a presystolic gallop rhythm. Moderate apical and aortic systolic murmurs were present. The blood pressure was 130/95. No other abnormalities were noted.

Course.—The patient obtained great relief from nitroglycerine and erythrol tetranitrate and a restricted mode of living. The physical findings remained essentially unchanged. The blood pressure was maintained at 150/100. Pulsus alternans developed in November, 1930, and persisted.

Electrocardiograms.—(Fig. 11.) Four routine electrocardiograms were taken. On November 12, 1929, a transition from normal conduction (Q-S 0.08, P-R 0.15) to left bundle-branch block (Q-S 0.12-0.16, P-R 0.15) was recorded in Lead I and the reverse transition occurred in Lead II, after which normal conduction persisted through Lead III. The rate during block ranged from 86 to 92 while during normal conduction it varied between 75 and 80. In December, 1929, normal conduction was recorded in all leads. In May, 1930, there was slight delay in intraventricular conduction (Q-S 0.10-0.11). On August 5, 1931, normal conduction was present in all three leads. There was moderate left axis deviation with diphasic T-waves in Lead I and a coronary type of inversion of the T-waves in Leads II and III, with slightly high origin of the latter in the tracings not distorted by branch block.

Diagnosis.—Hypertensive and coronary heart disease. Angina pectoris.

Comment.—In this instance the clinical and electrocardiographic evidence indicates that insufficiency of the coronary blood supply to the conducting tissue was responsible for the branch block.

In addition to the thirteen cases of paroxysmal bundle-branch block presented above we have collected from the literature fifty-eight additional cases, not of the Wolff, Parkinson, and White type, making a total of seventy-one.* They have been tabulated with the available data in Table I. Sixty-five of these seventy-one cases present clear evidence of heart disease. In Case 1 of our group and in five others (Cases 16, 30, 49, 50, 51) the classical features of cardiac disease were absent and on that account we have excluded them from the following analysis although we believe that the bundle-branch block was in itself evidence of heart disease. Of the remaining sixty-five patients there were thirty-five males, twenty-nine females, and one case in which the sex was not recorded. Thirty-six were over fifty years of age, twenty-six were fifty years of age or under, and in three the age was not recorded. Coronary or hypertensive heart disease was present in forty-four, thirty-three of whom were over fifty years of age; chronic rheumatic heart disease was present in six whose ages ranged from thirty-two to fifty years. The etiology of the heart disease in the remainder was diphtheria, four; thyrotoxicosis, three; congenital, one; and obscure in seven. Left bundle-branch block was present in sixty of the sixty-five cases. It is of interest that there were no instances of right bundle-branch block among the rheumatic cases. In twenty-five patients moderate to severe cardiac failure was associated with the period of block.

*The case reported by Faulkner¹⁵ as due to a rheumatic infection has not been included because subsequent records indicate that it is of the Wolff, Parkinson, and White type.

SUMMARY OF CASES

NUMBER	AUTHOR	AGE	SEX	DIAGNOSIS	BLOCK TRANSIENT	BLOCK RECURRENT	TRANSITION RECORDED BY E.C.G.	BRANCH AFFECTED	VAGAL STIMULATION EFFECTIVE	TIME BETWEEN ONSET OF B.B.B.* AND DATE WHEN PATIENT WAS LAST SEEN		NOTES
										LIVING	DEAD	
1	Case 1	41	F	Acute rheumatic fever		+	+	Rt.	+	18 mo.		C.S.P. slowed rate and transformed B.B.B. to normal. Later B.B.B. per- sistent.
2	Case 2	38	F	Myocarditis, ? rheumatic		+	+	Lt.	-	13 mo.		B.B.B. associated with cardiac failure. During controlled observations B.B.B. associated with faster rates. C.S.P. did not induce B.B.B.
3	Case 3	51	F	Hypertensive heart disease		+		Lt.	-	12 mo.		C.S.P. failed to change B.B.B. to normal or vice versa.
4	Case 4	56	M	Hypertensive heart disease	+			Lt.	-	4 mo.		B.B.B. associated with cardiac failure. C.S.P. had no effect on normal conduc- tion.
5	Case 5	50	M	Chronic rheumatic heart disease		+		Lt.	-	52 mo.		B.B.B. associated with transient complete A-V dissociation. Both later became persistent. Autopsy: Fibrosis in upper part of septum. Death from acute rheumatic carditis.
6	Case 6	57	M	Coronary throm- bosis	+			Lt.		2 mo.		B.B.B. and complete A-V dissociation dis- appeared in 24 hours.
7	Case 7	54	F	Hypertensive and coronary heart disease		+	+	Lt.		10 mo.		B.B.B. not associated with clinical con- dition.

*B.B.B.—Bundle-branch block. C.S.P.—Carotid sinus pressure.

8	Case 8	41	M	Hypertensive and coronary heart disease	+				Lt.	-	24 mo.		B.B.B. for 19 mo., normal conduction for next 5. B.B.B. not associated with clinical condition. C.S.P. had no effect on normal conduction.
9	Case 9	44	F	Hypertensive heart disease		+			Lt.		20 mo.		Autopsy: Myocardial scarring.
10	Case 10	45	F	Chronic rheumatic heart disease		+	+		Lt.		6 mo.		B.B.B. associated with transient idioventricular rhythm and cardiac failure. Auricular fibrillation also present. Autopsy: Chronic rheumatic heart disease.
11	Case 11	65	M	Coronary thrombosis	+				Lt.		1½ mo.		B.B.B., complete, and partial A-V dissociation associated with coronary thrombosis (posterior type). Normal rhythm and conduction resumed.
12	Case 12	55	F	Hypertensive heart disease	+				Lt.		2 mo.		B.B.B. associated with cardiac failure.
13	Case 13	75	F	Hypertensive and coronary heart disease	+		+		Lt.		23 mo.		
14	Azpitar ¹	62	M	Coronary heart disease	+				Lt.				B.B.B. observed on one day, absent on the following. Associated with probable coronary thrombosis.
15	Bagnaresi ²	58	M	Hypertensive and coronary heart disease; ? coronary thrombosis		+	+		Lt.	+	18 mo.		C.S.P. and ocular pressure slowed heart and abolished B.B.B. Bellafoline (slowed heart) and lacarnol abolished B.B.B. Amyl nitrite ineffective (rate increased).
16	Baker ³	75	M	Transient auricular fibrillation		+	+		Lt.		42 mo.		Normal at slow rates, B.B.B. at rapid rates. Oxygen inhalation abolished B.B.B.
17	Boas ⁶	63	F	Calcaneous aortic stenosis; angina pectoris		+	+		Lt.				Conduction probably dependent on state of coronary circulation.

SUMMARY OF CASES—CONT'D

NUMBER	AUTHOR	AGE	SEX	DIAGNOSIS	BLOCK TRANSIENT	BLOCK RECURRENT	TRANSITION RECORDED BY E.C.G.	BRANCH AFFECTED	VAGAL STIMULATION EFFECTIVE	TIME BETWEEN ONSET OF B.B.B.* AND DATE WHEN PATIENT WAS LAST SEEN		NOTES
										LIVING	DEAD	
18	Bousfield ⁷		M	Aortic regurgitation, ? etiology; angina pectoris	+			Lt.				B.B.B. associated with attack of angina pectoris.
19	Campbell ⁸	48	F	Chronic rheumatic heart disease		+		Lt.				B.B.B. associated on three occasions with cardiac failure, disappeared on improvement.
20	Campbell and Suzman ⁹	52	M	Hypertensive and coronary heart disease		+		Lt.			42 mo.	B.B.B. associated with cardiac failure on two occasions, later became persistent.
21	Caravatio ¹⁰	38	M	Coronary thrombosis		+		Lt.		6 mo.		B.B.B. persistent during last 3 mo.
22	Carr ¹¹	52	M	Coronary heart disease; ? coronary thrombosis		+	+	Lt.	+		44 mo.	C.S.P. and deep inspiration slowed heart and abolished B.B.B.
23	Cowan and Ritchie ¹²	43	M	Chronic rheumatic heart disease	+			Lt.				B.B.B. associated with cardiac failure and rapid heart rate. E.C.G.'s in Hill's report. ²²
24	Dresslor ¹³ Fig. 48	57	F	Coronary heart disease	+			Lt.				B.B.B. associated with cardiac failure.
25	Fig. 157	48	M	Coronary heart disease		+		Lt.				Exercise and increase in heart rate induced B.B.B.
26	Fig. 159	50	F	Hypertensive heart disease		+		Lt.				B.B.B. associated with cardiac failure. Periods of 2:1 B.B.B.

*B.B.B.—Bundle-branch block. C.S.P.—Carotid sinus pressure.

SUMMARY OF CASES—CONT'D

27	Elliot and Nuzum ¹⁶	66	M	Coronary heart disease		+	+	Lt.	+	48 mo.		Partial A-V dissociation. Normal complexes after dropped beats. C.S.P. slowed heart and abolished B.B.B. Exercise did not induce B.B.B. Later complete A-V dissociation.
28	Freundlich ¹⁹ Case 1	67	F	Hypertensive heart disease		+	+	Lt.	+			C.S.P. slowed heart and abolished B.B.B. In Case 1, B.B.B. associated with cardiac failure. (Two similar cases mentioned without details.)
29	Case 2	63	F	Coronary heart disease		+	+	Lt.	+			
30	Herrmann and Ashman ²¹ Case 1	55	F	Obscure		+	+	Lt.	+		30 mo.	Indirect vagal action (deep inspiration) slowed heart and abolished B.B.B. Exercise induced B.B.B. In Case 2, B.B.B. associated with cardiac failure.
31	Case 2	47	F	Hypertensive and coronary heart disease		+	+	Lt.	+	26 mo.		
32	Case 3	37	F	Chronic rheumatic heart disease; acute endocarditis; pregnancy		+	+	Lt.		7 mo.		Normal conduction associated with rest.
33	Case 4	60	M	Coronary heart disease		+	+	Lt.				Disappearance of B.B.B. seemed to be associated with clinical improvement.
34	Case 5	65	M	Coronary heart disease		+	+	Lt.				B.B.B. associated with cardiac failure.
35	Hill ²²	52	F	Thyrotoxicosis		+		Lt.				B.B.B. disappeared 2 mo. after thyroidectomy and reappeared 1 mo. later. Auricular fibrillation present until 1 mo. after operation.
36	Hubert ²⁴	38	M	Diphtheria	+			Lt.				B.B.B. present for 6 mo.
37	von Kapff ²⁵	45	M	Hypertensive heart disease	+			Lt.				B.B.B. associated with cardiac failure.

SUMMARY OF CASES—CONT'D

NUMBER	AUTHOR	AGE	SEX	DIAGNOSIS	BLOCK TRANSIENT	BLOCK RECURRENT	TRANSITION RECORDED BY E.C.G.	BRANCH AFFECTED	VAGAL STIMULATION EFFECTIVE	TIME BETWEEN ONSET OF B.B.B.* AND DATE WHEN PATIENT WAS LAST SEEN		NOTES
										LIVING	DEAD	
38	Kelly ²⁶	61	F	Hypertensive heart disease		+		Lt.				2:1 B.B.B. associated with cardiac failure. Complete and persistent B.B.B. appeared after a few days.
39	Kurtz ²⁷											
40	Case 1	73	M	Coronary heart disease	+			Lt.		5 mo.		No cardiac symptoms.
41	Case 2	61	F	Coronary heart disease; coronary thrombosis	+			Lt.		3 mo.		
42	Case 3	66	M	Hypertensive heart disease		+		Lt.		10 mo.		Associated with cardiac failure on two occasions.
43	Case 4	65	M	Coronary heart disease		+	+	Rt.			24 mo.	Associated with cardiac failure.
44	Case 5	56	F	Hypertensive heart disease		+		Lt.				B.B.B. not associated with change in clinical condition. (Insufficient evidence presented for diagnosis of rheumatic heart disease.)
	Case 6	54	F	Hypertensive and coronary heart disease		+	+	Lt.				B.B.B. associated with cardiac failure. Transient complete and partial A-V dissociation in addition.

*B.B.B.—Bundle-branch block. C.S.P.—Carotid sinus pressure.

SUMMARY OF CASES—CONT'D

NUMBER	AUTHOR	AGE	SEX	DIAGNOSIS	BLOCK TRANSIENT	BLOCK RECURRENT	TRANSITION RECORDED BY E.C.G.	BRANCH AFFECTED	VAGAL STIMULATION EFFECTIVE	TIME BETWEEN ONSET OF B.B.B.* AND DATE WHEN PATIENT WAS LAST SEEN		NOTES
										LIVING	DEAD	
55	Robinson ³⁷	63	M	Coronary heart disease	+			Lt.				B.B.B. associated with auricular fibrillation and cardiac failure. Heart rate 135. Digitalis slowed rate and B.B.B. disappeared. Six weeks later rate 158 but I-V conduction normal.
56	Ross ³⁸			Coronary heart disease		+	+	Lt.	+			C.S.P. and amyl nitrite abolished B.B.B.
57	Slater ⁴¹	40	F	Thyrotoxicosis		+		Lt.				"Myocardial involvement," 3:1 and 4:1 B.B.B. becoming complete and persistent after a few hours.
58	Stecker ⁴³	5	M	Diphtheria	+			Lt.			1 mo.	
59	Case 3	13	F	Diphtheria	+			Lt.				B.B.B. disappeared within two weeks.
60	Case 5	7	M	Diphtheria	+			Lt.				B.B.B. disappeared within eight days.
61	Steidl ⁴⁴	65	F	Hypertensive and coronary heart disease		+		Lt.		66 mo.		
62	Stenstrom ⁴⁵ Case 3	50	F	Transient auricular fibrillation		+	+	Lt.				Associated with cardiac failure. B.B.B. dependent on rate. Induced by exercise, abolished by rest.

SUMMARY OF CASES—CONT'D

63	Stenstrom ⁴⁷ Case 1		M	Coronary and hypertensive heart disease		+	+	Lt.	+	7 mo.		C.S.P. slowed the heart and changed B.B.B. to normal. Later persistent B.B.B. with no effect produced by C.S.P.
64	Case 2	42	F	Hypertensive heart disease		+	+	Lt.	+	48 mo.		C.S.P. slowed the heart and changed B.B.B. to normal. Exercise trans- formed normal QRS to B.B.B. 2:1 B.B.B. was present at times.
65	Case 3	70	F	Coronary and hypertensive heart disease		+	+	Rt.	-	3 mo.		One tracing (Fig. 23) suggests 2:1 B.B.B. B.B.B. associated with heart failure.
66	Willius and Anderson ⁵¹	63	M	Hypertensive heart disease		+	+	Lt.		39 mo.		Delayed A-V conduction with B.B.B.
67	Willius and Keith ⁵² Case 1	65	F	Hypertensive and coronary heart disease		+		Lt.		60 mo.		B.B.B. later became persistent.
68	Case 2	66	F	Coronary heart dis- ease; ? coronary thrombosis		+		Lt.		14 mo.		B.B.B. associated with cardiac failure.
69	Case 3	46	M	Hypertensive and coronary heart disease	+			Lt.		18 mo.		B.B.B. associated with cardiac failure.
70	Wood, Jeffers, and Wol- ferth ^{53, 59}	19	M	Congenital heart disease		+	+	Rt.		36 mo.		Interventricular septal defect. Transi- tion to normal conduction for 3 cycles.
71		55	M	Auricular fibrilla- tion	+			Rt.				

The finding of permanent bundle-branch block is often considered to be of grave prognostic significance. Recent reports,^{17, 48, 49, 58} however, indicate that this conduction disturbance per se does not necessarily have the unfavorable influence on prognosis often attributed to it. An attempt was made to follow up the reported cases of paroxysmal bundle-branch block but insufficient data were available to warrant drawing definite conclusions. In general, however, the prognosis in paroxysmal as in permanent bundle-branch block seems to be dependent upon the type and severity of the associated heart disease.

DISCUSSION

Association of Paroxysmal Bundle-Branch Block With Coronary and Hypertensive Heart Disease.—This is the largest group. The organic basis of the block in these cases is probably either arteriosclerotic narrowing in the coronary vessels supplying the conduction tissue, with or without partial permanent damage to a bundle branch,^{*} or the direct or indirect effects of an acute coronary thrombosis. Changes in the conducting fibers accompanying failure of the myocardium may be the primary or an additional factor in the production of the branch block.

The above statements, although at present impossible of absolute proof, are based upon more than hypothetical grounds. It is known that high degrees of A-V dissociation, sometimes transient in character, are observed in cases in which careful histopathological investigation of the conduction system shows partial or no damage. Of some significance are the clinicopathological findings in three cases by Géraudel²⁹ in which he claimed that permanent and transitory A-V dissociation could be associated with arteriosclerotic narrowing of the artery supplying the conducting tissue, without recognizable damage to the bundle of His. It is not absolutely clear, however, that Géraudel examined the bundle branches as carefully as the main bundle so that bilateral bundle-branch lesions which could have produced the complete A-V dissociation may have been overlooked. Of more significance is the finding of transient increases in intraventricular conduction time,³⁴ and in one case (Case 18), transient bundle-branch block itself, associated with attacks of angina pectoris. In accordance with the current concepts of angina pectoris these electrocardiographic changes must be attributed to anoxemia of the conducting tissue. Oxygen inhalation (Case 16) and amyl nitrite (Cases 49, 56) have transformed bundle-branch block to normal conduction. Further, the association of bundle-branch block with the clinical evidence of severe heart failure and the return to normal intraventricular conduction with better myocardial function has been observed frequently.

*Yater³⁰ believes that there is partial fibrosis of one or both bundle branches in all cases of intermittent block.

Thus, although the *precipitating* factor of the bundle-branch block may be physiological in some cases, the *fundamental cause* in cases of this group is organic heart disease directly or indirectly affecting a bundle branch. These cases are far more common than they are usually considered to be and in some the intermittent block is undoubtedly the precursor of permanent branch block. Consequently paroxysmal bundle-branch block which, like permanent bundle-branch block, may be the only evidence of organic heart disease, is of considerable significance, a fact which is not conveyed by the term "functional."

Association with Chronic Rheumatic Heart Disease.—Transient or intermittent bundle-branch block may occur less frequently in younger individuals with chronic heart disease of rheumatic origin. In all of these cases the periods of block have coincided with periods of poor myocardial function as manifested by cardiac failure, except in Case 5 in which such block is attributed to progressive fibrosis. The bundle and its branches are actually only specialized portions of the ventricular myocardium and it seems reasonable to assume that their function may be disturbed in the same way and at the same time as that of the myocardium.

Association With Acute Infections.—Transient bundle-branch block has been repeatedly attributed to acute infections and particularly to an active rheumatic process. Diphtheria on rare occasions can cause this type of transient conduction disturbance. Transient partial and complete A-V dissociation in otherwise clinically normal hearts is known to occur on rare occasions during acute infections, but we could find no conclusive evidence that acute infection, other than diphtheria, has directly caused a transient bundle-branch block.

With an active rheumatic infection in the presence of chronic rheumatic heart disease it is unjustifiable to attribute a transient bundle-branch block solely to a specific action of the acute process on the conducting tissue and to ignore the effects of the chronic lesion. In every case reported in which the transient branch block could be related in any way to an active rheumatic infection there was evidence of chronic valvular disease and poor myocardial function. After examining these cases critically it seems to us that there is more evidence to favor the opinion that infection usually acts largely through its effects on the whole myocardium including the bundle branches rather than specifically on a bundle branch or the blood supply of that branch. Rheumatic arteritis affecting a bundle branch may, however, be considered as a possible infrequent etiological factor as, perhaps, in Case 1 which is the best instance of a paroxysmal bundle-branch block being associated solely with an acute rheumatic infection. In Cases 2 and 10, although an infection was present, there was an obvious correlation between the branch block and dysfunction of the myocardium. In over 5,000 electrocardio-

grams taken at the House of the Good Samaritan in Boston on approximately 1,500 carefully followed patients with active rheumatic infection, no instance of transient bundle-branch block has been observed by Dr. T. Duckett Jones.

Association with Drugs.—Temporary bundle-branch block has been said to appear occasionally during the administration of drugs in the treatment of heart disease, particularly digitalis and quinidine. This has been shown to be the case with quinidine⁵⁰ but we could find no evidence that digitalis might have this effect.

Vagal Influences.—It is well known that the vagus nerves supply fibers to the S-A and A-V nodes and that carotid sinus pressure acting reflexly through the vagi may produce varying degrees of block in either node. The vagus has also been credited with the ability to depress conduction through the bundle branches.^{13, 32, 39} The type of bundle-branch block described by Wolff, Parkinson, and White may be induced by carotid sinus pressure^{20, 53, 57*} but, if the explanation of Holzmänn and Scherf²³ and of Wolferth and Wood⁵⁶ for its mechanism be accepted, this is not a true bundle-branch block and increase in vagal tone must act on the A-V node inhibiting the transmission of impulses over the normal pathway and forcing their passage by way of the short-circuiting bundle. As regards true bundle-branch block we have been unable to find any published evidence that sustained inhibition of bundle-branch conduction can be produced by vagal stimulation, nor have we been able to induce such inhibition in our own cases in whom bundle-branch block was previously present (Cases 2, 3, 4, 8). During periods of marked S-A slowing or A-V dissociation produced by mechanical vagal stimulation or after the administration of acetyl- β -methylcholine occasional broad complexes may appear which have been interpreted as showing bundle-branch block.^{13, 42} We believe that these are escaped beats of idioventricular origin because there is usually either absence of correlation between the P-waves and these wide QRS complexes or the P-R intervals are shortened, when in the presence of vagal stimulation unchanged or lengthened P-R intervals would be expected. However, in Case 8 on each of two occasions during marked S-A slowing without A-V dissociation produced by carotid sinus pressure single broad complexes occurred which were similar to those recorded during periods of bundle-branch block and whose P-R intervals were of the same length as those of the neighboring normal complexes (Fig. 12). For these reasons we believe that these two complexes may be examples of bundle-branch block rather than of ventricular escape. This provides evidence that the vagi may exert a direct influence upon bundle-branch conduction as is suggested

*The case reported by Wilson⁵³ displays the characteristics of the Wolff, Parkinson, and White type. Wilson found during the stimulation phase following the subcutaneous injection of atropine an alteration in the form of the QRS complex which he considered suggestive of branch block. There was, however, no increase in the Q-S interval.

by Daniélopou and his associates¹⁴ and Sigler⁴⁰ who found that intraventricular conduction may be slightly increased during carotid sinus stimulation.

It has been shown by animal experiments that when only a narrow strip of conducting tissue exists conduction is normal at slow rates but at rapid rates it is impaired.⁵ Our results in Case 1, supported by the experience of others, suggest that intermittent bundle-branch block may be changed to normal conduction under vagal influences through the cardiac slowing induced by the increase in vagal tone. As in Cases 1 and 2 an increase in heart rate produced by a decrease in vagal tone or by any other means may in some cases be expected to produce branch block by further depressing the bundle branch.

A bundle branch may be partially damaged by progressive changes incident to myocardial failure or to inadequate metabolic exchanges resulting from poor coronary circulation to the conducting tissue, whether

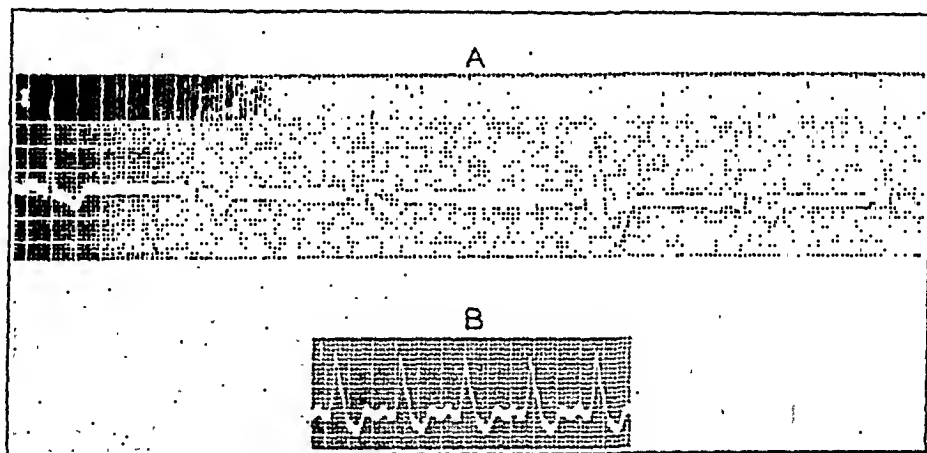


Fig. 12.—Case 8. *A*, (Jan. 15, 1937) single complex simulating left bundle-branch block occurring during right carotid sinus pressure which produced marked cardiac slowing. This record begins 9 sec. after the application and ends 6.5 sec. before the removal of the pressure. *B*, (Dec. 15, 1935) left bundle-branch block for comparison. Time-marker 0.20 and 0.04 sec.

there is partial fibrosis or not. Under such conditions the bundle branch may be able to conduct impulses within certain limits of rate but its conductivity will be impaired when the rate rises above a critical level. It is evident that the critical level will be dependent upon the degree of depression in the conducting fibers and it is not unreasonable to assume from the nature of the factors producing the inhibition that this may disappear or that the degree of depression may fluctuate or, in the case of fibrosis, progress. By accepting such a view it is possible to explain respectively transient bundle-branch block (Cases 4, 6, 8, 11, 12, 13), intermittent bundle-branch block (Cases 1, 2, 3, 5, 7, 9, 10) and intermittent progressing to persistent bundle-branch block (Cases 1, 5). In the routine records of our cases there was no constant correlation between the cardiac rate and the degree of intraventricular conduction. So long as the degree of depression may fluctuate it is not surprising that such a correlation was frequently not evident.

In the past emphasis has been placed upon the vagal influences when they were effective in converting bundle-branch block to normal conduction. In these cases, particularly, there has been the tendency to use the term "functional bundle-branch block." If heart disease is present or suspected these vagal influences, although dramatic, are not to be used as criteria in classifying the branch block. It should be clearly recognized that changes in the conducting tissue incident to organic heart disease constitute the fundamental and the significant cause of the paroxysmal bundle-branch block.

Mechanism.—The mechanism of this conduction disturbance has been discussed in previous reports and the terms "incomplete" or "partial" bundle-branch block applied.^{21, 22, 45, 46, 47} A further consideration of the underlying mechanism seems desirable in the light of our present experience.

It is not necessary that complete block exist in one branch in order that impulses be forced to travel through the opposite branch and the myocardium to reach the affected ventricle. Conduction by this pathway may be necessary when one branch is only depressed. So long as the conduction time through the damaged branch is greater than that through the intact branch* plus the myocardial pathway between the two ventricles, the affected ventricle is activated by an impulse traveling through the latter channels, and bundle-branch block complexes result. Whenever the conduction time through the damaged branch passes the critical level and becomes shorter than that through the channel just mentioned, normal QRST complexes appear. It is therefore apparent that if conduction through the affected branch is close to this critical zone small changes in the conductivity of the depressed branch result in sudden and complete changes in the form of the ventricular complexes. Such small changes in conductivity result, for example, from the increase or decrease in diastolic rest due to slight alterations in heart rate as in Cases 1 and 2. In instances of 2 to 1, 3 and 4 to 1 bundle-branch block (Cases 26, 38, 46, 57), by a mechanism similar to that in partial A-V dissociation, the conduction of one or two impulses through the damaged branch increases the refractory period of that branch so that the succeeding impulse is delayed beyond the critical level and a branch block complex appears. The resulting rest permits the normal conduction of the next one, two, or three complexes.

When severe myocardial failure or coronary thrombosis is the cause of temporary bundle-branch block, conduction through the affected branch is severely depressed or even temporarily abolished. As improvement occurs the potential conduction time becomes progressively shorter

*It is known that lesions in both branches are frequently found in cases exhibiting bundle-branch block. The mechanism, however, would not be altered by damage or depression of both branches. Conduction in such instances would take place through the less damaged branch.

but branch block complexes remain until it passes below the critical level at which time normal complexes suddenly appear.

The complexes of the intermediate type which have been recorded during transitions, e.g., in Cases 2 and 10, probably occur when the conduction time through the damaged branch falls within the critical zone and is approximately equal to that through the intact branch plus the myocardium. The ventricle on the affected side is then partly activated by impulses which have passed along both routes.

SUMMARY

1. Due to the more common use of the electrocardiograph instances of paroxysmal bundle-branch block are becoming a more frequent finding. It is important to recognize the fundamental cause of the branch block in these cases and to differentiate clearly the inconsequential type from the group in which changes in the junctional tissue incident to heart disease are primarily responsible for the conduction disturbances.

2. The former group consists mainly of cases in which the QRS complex is wide and the P-R interval is abnormally short (Wolff, Parkinson, and White). This finding is no indication of heart disease.

3. Significant are the cases in which changes in the conduction tissue are a direct or indirect result of organic heart disease. Pathological processes, not necessarily permanent, in a branch of the bundle of His such as are associated with myocardial failure, coronary insufficiency, and coronary thrombosis, with or without partial fibrosis of a branch, are primarily responsible for transient or recurrent bundle-branch block. Although physiological changes may act as precipitating factors it should be recognized that these are effective only in the presence of actual changes in the conducting tissue. It is doubtful whether an acute infectious process other than diphtheria can cause transitory branch block; perhaps very rarely a rheumatic infection may so act.

4. Fifty-eight cases of paroxysmal bundle-branch block were found reported in the literature and to these we have added thirteen new cases. Of the seventy-one patients there was clear evidence of heart disease in sixty-five, of which thirty-five were males, twenty-nine were females, and one was of unrecorded sex. The six patients without other evidence of heart disease are excluded from the analysis although we consider the presence of paroxysmal bundle-branch block in itself evidence of heart disease. Coronary or hypertensive heart disease was present in forty-four patients while chronic rheumatic heart disease was present in six. The etiology of the heart disease in the remaining fifteen patients was diphtheria in four; thyrotoxicosis in three; congenital in one; and obscure in seven. Left bundle-branch block was present in sixty of the sixty-five patients. Moderate to severe heart failure was associated with the branch block in twenty-five patients.

5. The effects of changes in vagal tone were studied in six of our cases. Single bundle-branch block complexes were obtained during vagal stimulation on two occasions in one of these. Our experience and the published data show that increase in vagal tone does not produce sustained inhibition of bundle-branch conduction. Variations in vagal tone affect the conduction only by decreasing or increasing the cardiac rate to such an extent that the depressed branch becomes capable or incapable of transmitting impulses.

6. The mechanism of "partial" or "incomplete" bundle-branch block is discussed in the light of present experience.

7. We conclude that paroxysmal bundle-branch block (without a very short P-R interval) is as a rule a sign of serious heart disease, most often due to coronary sclerosis but in some cases associated with rheumatic heart disease, diphtheria, and factors that cannot clinically be ascertained. It is doubtless more common than it has been thought to be; serial electrocardiograms taken during myocardial (congestive heart) failure, coronary insufficiency, and elevated heart rates may reveal transient defects in bundle-branch conduction.

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A CORRELATION OF THE FLUOROSCOPIC, CLINICAL, AND POST-MORTEM FINDINGS IN 155 CASES OF ORGANIC HEART DISEASE*

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RADIOGRAPHY of the heart is a basic diagnostic procedure which complements and augments information derived from physical examination and electrocardiography. Many attempts to estimate the size of the heart accurately have been made by radiologists ever since teleroentgenography became an accepted procedure. Within a comparatively short time correlations were evolved between the cardiac silhouette and various heart lesions. The surface area of the heart and the various cardiac diameters were compared with standards obtained by similar determinations made on normal individuals. The correlations vary from the cardiothoracic ratio to the ratio between the surface area of the cardiac silhouette and the surface area of the body, or the body weight or height.¹

The failing common to these procedures is that the heart is considered as a unit rather than as an organ composed of four interdependent chambers. Thus they are of value in determining enlargement of the heart taken as a whole but offer no reliable data concerning the status of the individual chambers. Inasmuch as the clinical importance of determining enlargement of the several heart chambers is assuming significant proportions in the study of cardiac dynamics, a method which may be useful should receive careful consideration.

Fluoroscopic examination of the heart in the right and left anterior oblique positions and the postero-anterior position is a reliable method based on the effects of enlargement of each chamber on the border-forming portions of the heart shadow as seen in the various projections. It also takes into consideration the relationship of the heart to the esophagus and mediastinal structures.

The method is essentially one which offers qualitative rather than quantitative data in the sense that the findings are expressed in degrees of enlargement rather than numerically.

Among those who laid the groundwork for fluoroscopic examination of the heart may be mentioned Assman, Dietlen, Bordet, Vaquez, Roesler, Parkinson, Nemet, and others.²

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Most observations have been based on small series of cases, not all of which were proven at autopsy. At the suggestion of the late Geza Nemet we undertook to correlate the autopsy and cardioscopic findings in a series of cases sufficient for numerical analysis.

MATERIAL

This series collected over a period of six years consists of 155 cases of organic heart disease each of which had been fluoroscoped shortly before death. Thanks are due the department of pathology for observations made so that a reliable comparison could be made of the fluoroscopic and the autopsy findings.

The cases are divided into two groups, one consisting of 88 cases of valvular heart disorders of rheumatic origin, the other of 67 cases of nonvalvular heart disease including the cases of hypertension and cardiovascular disease with arteriosclerosis. The group of congenital heart disease cases was omitted because it was too small to be of value here. No mention is made of the great vessels in this report.

Clinical observations were made by various members of the medical division. As a rule the clinical diagnoses were based on the criteria laid down by the American Heart Association.

The age and sex incidence is summarized in Table I.

TABLE I
AGE AND SEX INCIDENCE

AGE	VALVULAR HEART DISEASE		NONVALVULAR HEART DISEASE	
	MALE	FEMALE	MALE	FEMALE
0-9	6	0	0	0
10-19	16	8	0	0
20-29	14	8	0	0
30-39	5	4	1	1
40-49	10	8	5	2
50-59	6	3	14	6
60-69	0	0	20	7
70-over	0	0	6	5

PROCEDURE

Fluoroscopies were done with the patient in the erect position. Observations were made in the right and left anterior obliques and the frontal positions. In each case the esophagus was visualized by means of barium paste* and the position of the trachea and main bronchi was determined. We did not use standard angles of obliquity since it was found that the optimum angle of visualization varied with the individual.

Chamber enlargements were recorded as maximal, moderate and no enlargement. No attempt was made to distinguish hypertrophy

*The barium paste was prepared by slowly adding water to precipitated barium sulfate while stirring vigorously. Enough water is added to make a fairly thick, smooth mixture. A small amount of chocolate syrup may be added for flavoring.

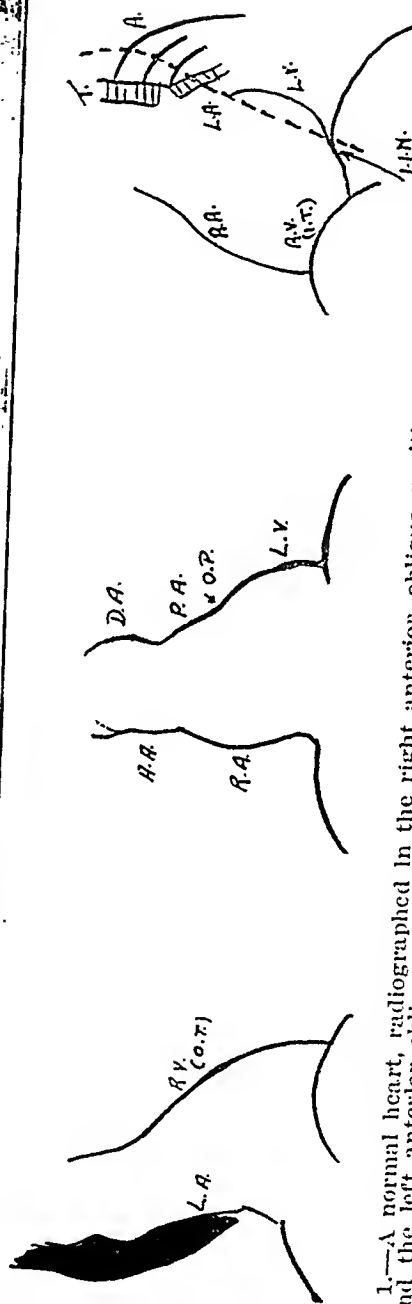
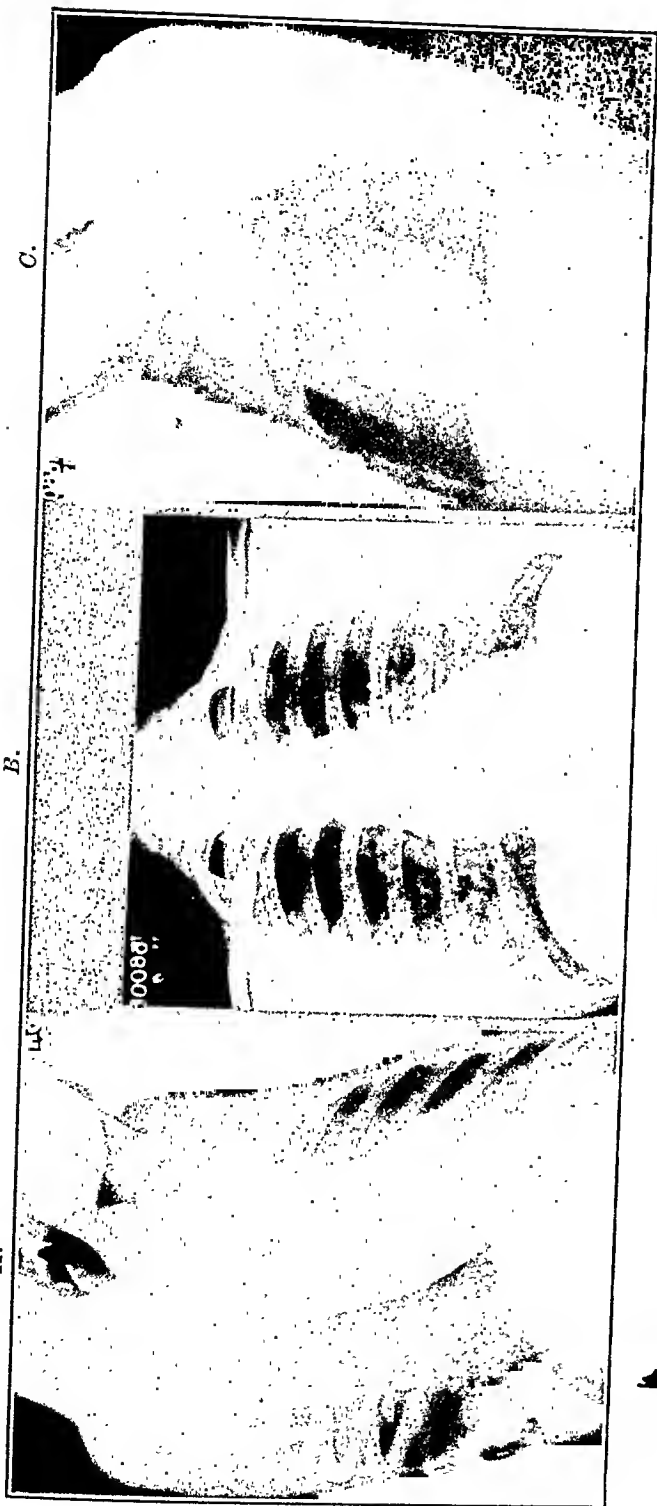


Fig. 1.—A normal heart, radiographed in the right anterior oblique position (A), the postero-anterior position (B), and the left anterior oblique position (C).
L.A.A., left auricle; *R.A.*, right auricle; *L.V.*, left ventricle; *R.V.* (*I.T.*), right ventricle, inflow tract; *R.V.* (*O.T.*), right ventricle, outflow tract; *O.P.*, oscillating point (the point of opposite pulsation between the right ventricle and left ventricle at the junction of the second and third left cardiac arcs; *I.L.N.*, inferior interventricular notch between the left ventricle and inflow portion of the right ventricle; *A.A.*, ascending aorta; *D.A.*, descending aorta.

Note the straight outline of the barium-filled esophagus in the right anterior oblique position, indicating no enlargement of the left auricle. The relationship of the anterior aspect of the heart to the anterior chest wall as seen in Fig. 1A and the left ventricle to the spine as seen in Fig. 1C should also be noted.

from dilatation fluoroscopically. Post-mortem observations of the size of the cardiac chambers were made in similar degree, and the evidences of valvular defects, muscle hypertrophy, and coronary artery disease were noted.

The data also were analyzed from other viewpoints. In the rheumatic group the chamber enlargements associated with various valvular defects were tabulated. The accuracy of the clinical diagnoses was determined by comparison with the autopsy findings. Ventricular thickness, the incidence of congestive heart failure, auricular fibrillation, and pericarditis were also noted.

In the nonvalvular group the incidence of hypertension, coronary artery disease, and heart failure was correlated with chamber enlargement, murmurs, valvular defects, and muscle thickness. The comparative accuracy of the clinical diagnoses was determined.

FLUOROSCOPIC CRITERIA

The criteria for estimating chamber enlargement in this study are those submitted by Nemet and adopted for inclusion in the *Criteria for Cardiac Diagnosis*.³ Additional refinements since evolved were taken into consideration.⁴

Briefly, the criteria are:

1. *Left Auricle*.—Protrusion of the left auricular shadow into the retrocardiac space displacing the barium-filled esophagus posteriorly, best seen in the right anterior oblique position. Deviation of the barium esophagus to the right in the frontal projection, found in more advanced cases of left auricular enlargement. Elevation and compression of the left main bronchus in the left anterior oblique position, indicative of vertical enlargement of the chamber. The presence of the right border of the left auricle just within the right cardiac border, or on the upper portion of the right cardiac border also may be determined fluoroscopically in the more advanced cases.

Moderate enlargement is believed present when posterior and horizontal enlargement is found. Maximal enlargement is indicated by the presence of posterior, horizontal, and vertical enlargement of more advanced degree.

2. *Left Ventricle*.—Increase in the length of the lower left cardiac are as measured from the point of opposite pulsation downward. Projection of the apex below the diaphragm during deep inspiration. Posterior bulging of the left ventricle into the retrocardiac space and depression of the inferior interventricular notch in the left anterior oblique position.

Moderate enlargement is manifested by posterior bulging of the ventricle with downward apical displacement. Maximal enlargement

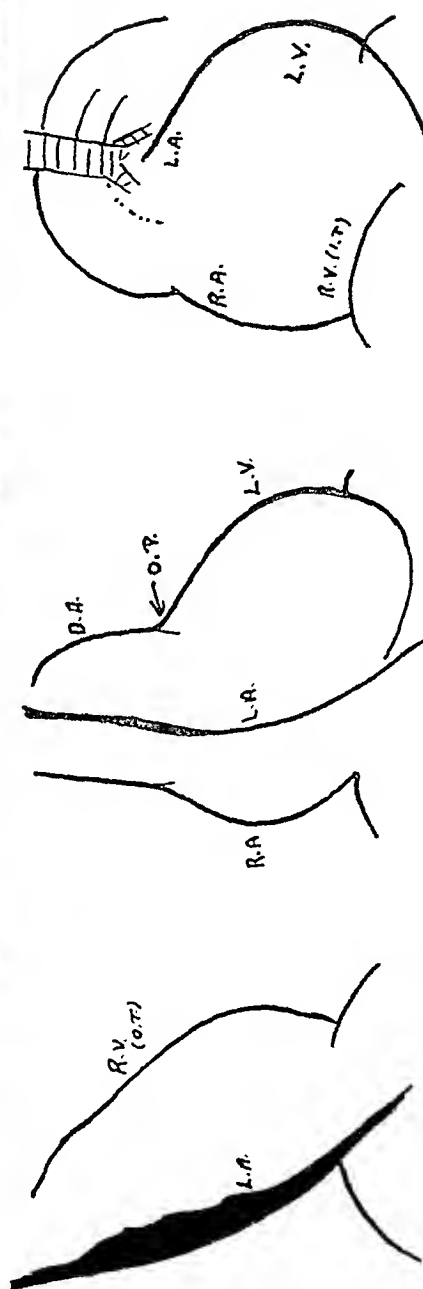
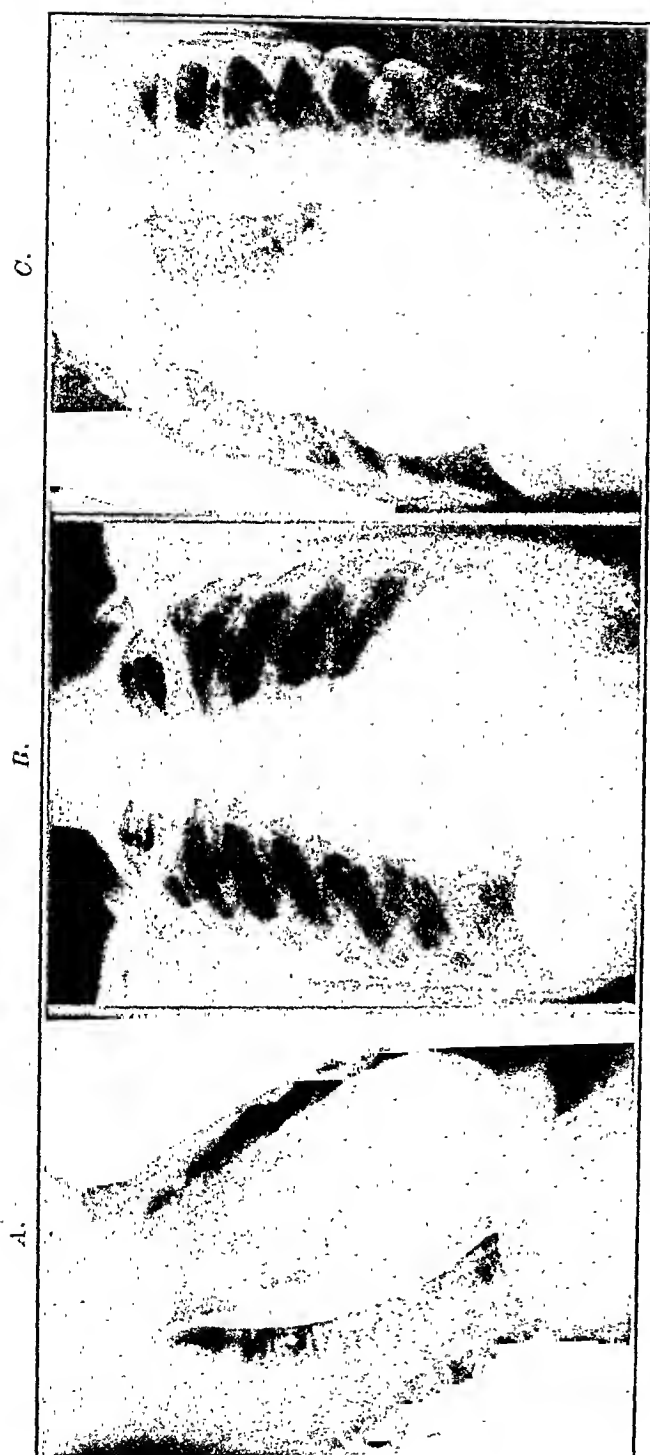


Fig. 2.—Enlargement of the left ventricle is maximal. The oscillating point is shifted upwards. Moderate enlargement of the right ventricle is demonstrable only in the right anterior oblique position, being obscured by the left ventricle in the anterior projection. The tremendous posterior bulge of the left ventricle is demonstrated in the left anterior oblique position.

implies massive posterior bulging and depression of the interventricular notch in the left anterior oblique view. The third left cardiac arc is lengthened, shifting the point of opposite pulsation upward.

3. *Right Auricle*.—Increase in the length of the right auricular appendix segment as seen in the left anterior oblique position. Increase in the acuity of the right atrioventricular angle in the left anterior oblique position. Increase in the posterior convexity of the right auricle in the right anterior oblique position so that the shadow of the barium esophagus passes through its opacity. This latter is indicative of enlargement of the body of the right auricle.⁵

Moderate enlargement is considered present when the right auricular segment is moderately increased and elevated. Maximal enlargement means enlargement of the auricular segment so that it assumes approximately a horizontal plane. When enlargement of the body of the chamber is present maximal enlargement is diagnosed.

4. *Right Ventricle*.—Increase in the length and convexity of the second left cardiac arc, depressing the point of opposite pulsation as seen in the frontal projection. Protrusion of the anterior aspect of the right ventricle into the retrosternal space in the right anterior oblique position (outflow tract).

Increase in the length of the diaphragmatic surface of the heart as measured from the right atrioventricular junction to the inferior interventricular notch as seen in the left anterior oblique position. Rotation of the right auricle upwards and posteriorly so that the right ventricle comes to form part of the lower right cardiac border in the frontal projection (inflow tract).

Moderate enlargement of the right ventricle is considered present when there is definite enlargement of the outflow tract. Maximal enlargement is diagnosed in the presence of both inflow and outflow tract enlargement.

CORRELATIONS OF THE RADIOSCOPIC, CLINICAL, AND POST-MORTEM FINDINGS

Valvular Group

1. *Left Auricle* (correlations possible in 88 cases).—Maximal enlargement was found at autopsy in 57 cases. Of these, 53 had been reported correctly fluoroscopically. The remaining four cases had been reported as moderately enlarged.

Moderate enlargement was found at autopsy in 20 cases. Eighteen of these had been reported correctly. Of the remaining two cases, one had been reported as maximally enlarged and one as not enlarged.

No enlargement was found in 11 cases, and was reported correctly in 10. The single case incorrectly diagnosed had been reported as moderately enlarged.

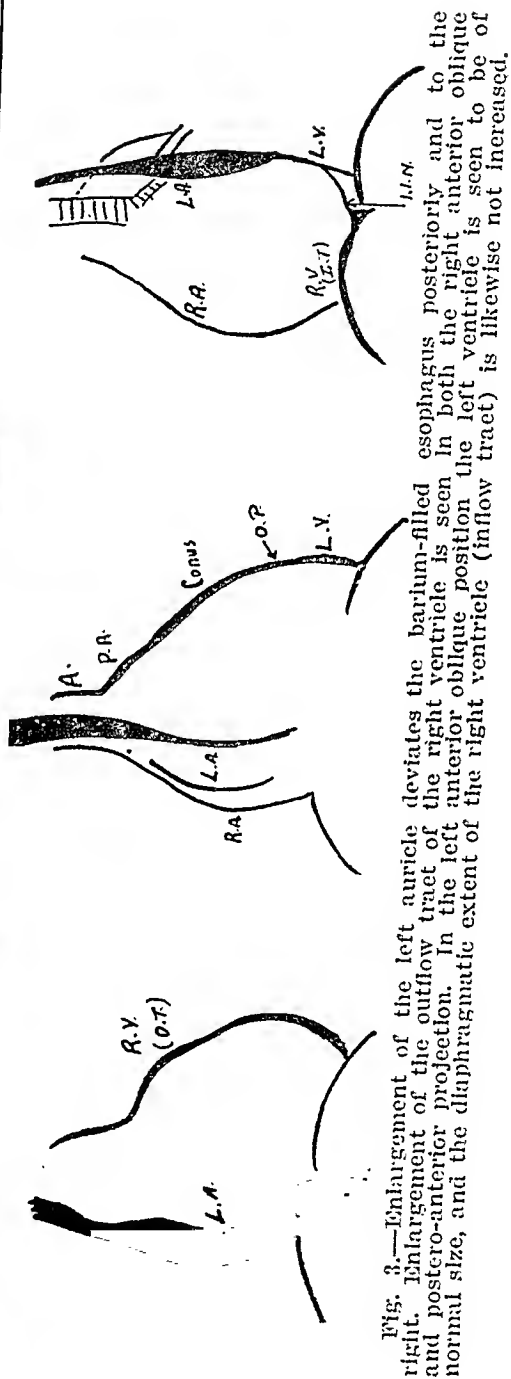
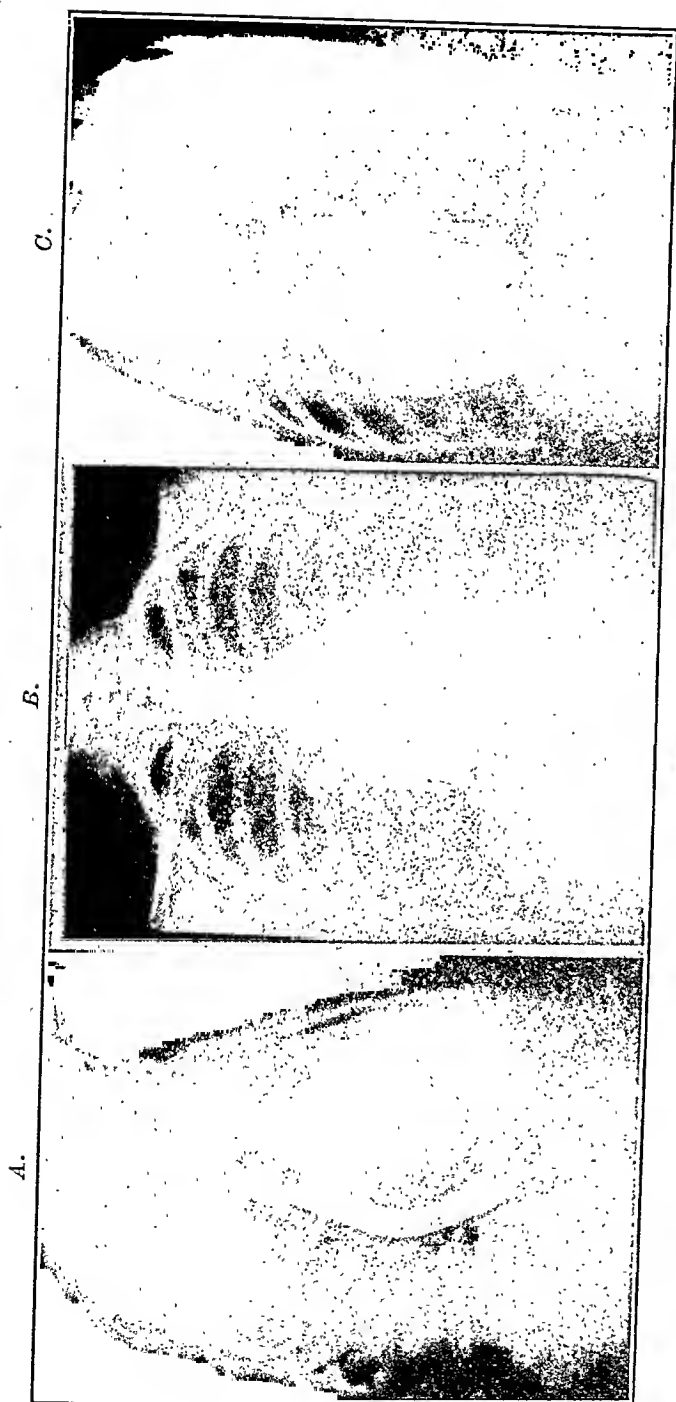


Fig. 3.—Enlargement of the left auricle deviates the barium-filled esophagus posteriorly and to the right. Enlargement of the outflow tract of the right ventricle is seen in both the right anterior oblique and postero-anterior projection. In the left anterior oblique position the left ventricle is seen to be of normal size, and the diaphragmatic extent of the right ventricle (inflow tract) is likewise not increased.

ventricles and found to have no enlargement at autopsy likewise were found to have predominant mitral pathology with maximal right ventricular enlargement.

Enlargement of the right ventricle first results in an increased prominence of its conus portion anteriorly. This is followed by rotation towards the left and upwards as the natural restraints of the pericardium, sternum, spine, lungs, and remaining cardiac musculature exert their influence. As enlargement of the right ventricle progresses, the left ventricle is displaced posteriorly, so that in the left anterior oblique position the left ventricular segment seems to be larger than it actually is.

In the frontal plane maximal enlargement of the right ventricle may result in such enlargement of the transverse diameter of the heart that the left cardiac border, formed almost entirely by the right ventricle, approximates the axilla. In these cases the left ventricle may be represented by a small demilune low on the left cardiac silhouette. We have seen cases in which the entire left border of the heart was formed by the right ventricle, the left ventricle being rotated so that it assumed a completely posterior position.

For these reasons a diagnosis of left ventricular enlargement in the presence of maximal right ventricular enlargement should be made only after careful determination of the point of opposite pulsation in the frontal position to determine the length of the left ventricular segment and localization of the inferior interventricular notch in the left anterior oblique position. A diagnosis of left ventricular enlargement should not be made unless there is definite elongation of the third left cardiac arc, depression of the inferior interventricular notch, or bulging into the retrocardiac space.

Errors in the estimation of the size of the right ventricle were less frequent. In reviewing the cases diagnosed incorrectly it was noted that the cases of maximal enlargement wrongly diagnosed as moderately enlarged all occurred in hearts with marked aortic lesions (three cases with aortic insufficiency and two with aortic stenosis) with maximal left ventricular enlargement.

Massive enlargement of the left ventricle masks coincident right ventricular enlargement by shifting the point of opposite pulsation upward, thereby shortening the apparent extent of the second left cardiac arc. In the right anterior oblique position the left ventricular mass may overshadow the anterior bulge of the right ventricle and obscure outflow tract enlargement.

It would seem, then, that special attention should be given to the retrosternal bulge of the cardiac contour in the right anterior oblique position before estimating the size of the right ventricle in the presence of maximal left ventricular enlargement. The diaphragmatic extent of the right ventricle should likewise be noted carefully.

Examination of the patient in deep inspiration may help visualize the inferior interventricular notch. Quite often this landmark cannot be located definitely, and this should be taken into consideration before conclusions are reached.

Clinical-Pathological Correlations

A clinical diagnosis of congestive failure was made in 81 cases, all of which were confirmed at autopsy. Of the seven patients without heart failure, three had subacute bacterial endocarditis, two had chronic nephritis, one had advanced hypertension, and one was a six-year-old child with active carditis.

Subacute bacterial endocarditis occurred in 12 cases. The mitral and aortic valves were equally involved. Congestive failure occurred in nine instances.

Seven patients, all in the age groups above forty, had myocardial infarcts.

The incidence of valvular lesions together with the resultant chamber enlargements is summarized in Table II. These findings were derived from the post-mortem observations.

Mitral valvular pathology alone was found in 14 cases, and aortic valve pathology alone was found in 12 cases. A double mitral lesion with a single aortic lesion (most often insufficiency) occurred 21 times, while a double aortic lesion with a single mitral lesion occurred but once. Double aortic and double mitral lesions occurred in 15 individuals. Tricuspid stenosis and insufficiency were associated with the double aortic and double mitral lesions three times. Tricuspid insufficiency in association with other valvular defects occurred 25 times, while a double tricuspid lesion occurred six times. A single aortic and single mitral lesion occurred ten times. Endocarditis of the pulmonary valve which did not produce an anatomic defect was found in five cases, all of which had coexistent panvalvulitis.

The average thickness of the right ventricular myocardium in the cases considered maximally enlarged (55 cases) was 6.5 millimeters. In this group maximal enlargement of the left ventricle occurred 28 times, moderate enlargement 22 times, and no enlargement 5 times. The average thickness of the left ventricular wall in this group was 16.0 millimeters.

The average thickness of the right ventricular myocardium in the cases considered moderately enlarged (25 cases) was 5.6 millimeters. In this group maximal enlargement of the left ventricle occurred 15 times, moderate enlargement 10 times, and no enlargement once. The average thickness of the left ventricular wall was 17.2 millimeters.

The average thickness of the right ventricular myocardium in the cases with no enlargement (8 cases) was 3.2 millimeters. In this group

TABLE II

LESION	NUMBER OF CASES	DEGREE OF ENLARGEMENT															
		RT. VENT.				LT. VENT.				RT. AURIC.				LT. AURIC.			
		MAX.	MOD.	NO	VENT. (MM.)	MAX.	MOD.	NO	VENT. (MM.)	MAX.	MOD.	NO	MAX.	MOD.	NO		
M.S., M.I., A.I.	10	8	2	0	5.9	8	2	0	16.9	5	2	0	9	1	0		
M.S., M.I., A.I., T.I.	10	9	1	0	7.3	6	3	1	15.3	5	3	0	9	1	0		
M.S., M.I., A.S., A.I.	8	2	5	1	5.7	4	4	0	18.6	1	3	2	3	2	3		
A.I.	8	2	3	3	4.6	6	2	0	18.4	3	2	0	4	0	4		
M.S., M.I., T.I.	6	5	1	0	6.3	3	2	1	15.5	3	1	1	5	1	0		
M.S., M.I.	6	5	1	0	6.0	0	6	0	11.5	2	2	1	4	2	0		
M.I., A.I.	5	2	2	1	5.4	5	0	0	18.6	1	0	1	4	3	0		
M.I.	5	2	2	1	5.8	1	2	2	13.0	1	1	2	2	3	0		
M.S., A.I.	4	2	1	1	7.7	1	3	0	15.2	2	1	0	1	3	1		
M.S., M.I., A.S., A.I., T.I.	4	0	3	1	5.0	2	1	1	16.2	0	4	0	3	1	0		
A.S.	3	2	1	0	7.3	3	0	0	17.3	1	1	0	2	1	0		
M.S.	3	3	0	0	6.3	1	2	0	13.3	3	0	0	3	0	0		
M.S., M.I., A.S., A.I., T.S., T.I.	3	3	0	0	6.0	2	1	0	17.0	3	0	0	2	1	0		
M.S., T.I.	2	2	0	0	5.5	0	1	1	17.0	2	0	0	2	0	0		
M.S., M.I., T.S., T.I.	2	2	0	0	5.0	0	1	1	16.5	1	1	0	2	0	0		
M.I., T.I.	2	2	0	0	4.5	1	1	0	10.5	1	0	0	2	0	0		
A.S., A.I.	1	0	1	0	4.0	1	0	0	20.0	0	0	1	0	0	0		
A.S., A.I., M.I.	1	0	1	0	5.0	0	1	0	15.0	0	0	1	0	0	0		
M.S., A.I., T.I.	1	1	0	0	6.0	0	1	0	13.0	1	0	0	1	0	1		
M.S., M.I., T.S., T.I., A.I.	1	1	0	0	7.0	0	1	0	15.0	0	0	0	1	0	0		

maximal enlargement of the left ventricle occurred three times, moderate enlargement twice, and no enlargement three times. The average thickness of the left ventricular wall was 16.2 millimeters.

The heaviest heart weighed 1,400 grams, the lightest 320 grams. The average weight was 750 grams. There did not seem to be any definite relationship between the heart weights and the patients' ages in this series. No definite relationship could be found between the valvular lesions and heart weights, although the various valvular defects seemed to produce constant changes in the sizes of the chambers. For instance, one heart weighing 1,050 grams had a double mitral lesion with tricuspid insufficiency, while a heart weighing 1,200 grams had an isolated aortic insufficiency. Still another heart with an isolated aortic insufficiency in a patient of the same age weighed but 400 grams. The heart weighing 1,400 grams had mitral stenosis with aortic insufficiency (Table III).

TABLE III

VALVE DEFECTS	HEART WEIGHTS (GM.) AND AGE OF PATIENT (YR.)			
M. S., M. I., A. I.	630 (16)	500 (38)	550 (29)	700 (17)
	520 (44)	500 (16)	600 (22)	
	450 (13)	560 (24)	350 (46)	
M. S., M. I., A. S., A. I.	550 (21)	550 (21)	480 (24)	
	480 (60)	480 (56)	400 (28)	
	450 (47)	730 (24)		
M. S., M. I., A. I., T. I.	550 (9)	400 (14)	550 (19)	
	1200 (17)	550 (29)		
	400 (12)	400 (24)		
A. I.	1000 (36)	540 (34)	730 (52)	
	680 (52)	850 (38)	850 (46)	
	360 (10)	400 (14)		
M. S., M. I., T. I.	450 (39)	600 (22)		
	360 (13)	1050 (20)		
	640 (44)	500 (18)		
M. S., M. I.	800 (52)	600 (7)		
	500 (21)	300 (48)		
M. I., A. I.	950 (22)	500 (11)	660 (15)	
	480 (47)	1100 (18)		
M. I.	500 (11)	550 (45)	350 (36)	
	320 (23)	290 (5)		
	310 (12)	720 (47)		
M. S., T. I.	290 (14)	1400 (22)		
M. S., A. I.	450 (49)	410 (34)		
M. S., M. I., A. S., A. I., T. I.	700 (17)	480 (40)		
	530 (52)	890 (46)	530 (52)	
A. S.	300 (28)	550 (40)	660 (42)	
M. S.	600 (21)	660 (23)		
M. S., M. I., A. S., A. I., T. S., T. I.	550 (24)			
M. S., M. I., T. S., T. I.	320 (46)			
A. S., A. I.	450 (54)			
A. S., A. I., M. I.	750 (13)	580 (8)		
M. I., T. I.	600 (22)			
M. S., A. I., T. I.	350 (14)			
M. S., M. I., T. S., T. I., A. I.				

Pericarditis was found in 38 cases at autopsy and was diagnosed during life in 12 cases. The poor clinical showing may be due to the fact that the 38 cases included both old and recent pericarditis, and

TABLE IV

FINDINGS	NUMBER OF CASES	DEGREE OF ENLARGEMENT													
		L.T. VENT.				R.T. VENT.				L.T. AURIC.			R.T. AURIC.		
		MAX.	MOD.	NO	VENT. (MM.)	MAX.	MOD.	NO	VENT. (MM.)	MAX.	MOD.	NO	MAX.	MOD.	NO
Hypertension, coronary artery disease, heart failure	28	22	6	0	17.3	6	16	6	5.5	3	15	8	3	11	7
Coronary artery disease, heart failure	13	2	9	2	14.0	2	6	5	5.6	0	3	9	0	1	6
Hypertension, coronary artery disease	8	5	3	0	17.4	0	5	3	4.3	0	3	5	0	1	4
Hypertension	8	4	4	0	20.5	1	1	6	4.2	0	2	6	0	1	7
Hypertension, coronary artery disease	4	3	1	0	21.0	1	3	0	6.2	0	3	1	0	3	0
Normal	4	0	1	3	12.0	0	0	4	3.0	0	0	4	0	0	4
Coronary artery disease	2	1	1	0	13.5	0	0	2	3.5	0	0	1	0	0	1

the patients may have been seen only during a quiescent stage. Twenty cases occurred in patients over twenty years old and 18 in patients under twenty. There was no definite predominance of any valvular lesions coincident with pericarditis.

There was complete agreement between the clinical and autopsy diagnoses in 32 cases. In 30 cases there was partial agreement (by partial agreement we mean that the valves involved were correctly diagnosed, but an error was made in the estimation of the presence or absence of either insufficiency or stenosis. For instance, a partial error was made in a case where a double mitral lesion with aortic insufficiency was diagnosed clinically and mitral and aortic insufficiency only was found at autopsy). In 16 cases the clinical diagnosis included more pathology than actually was present, and in 14 cases a valvular defect was omitted in the clinical diagnosis.

In 26 cases a complete error was made (by this we mean that a valvular defect was completely misdiagnosed. For instance, in a case where a double mitral lesion and aortic insufficiency was diagnosed during life, only an aortic insufficiency was found at autopsy).

Nonvalvular Group

This series consists of 67 cases. The incidence of hypertension, coronary artery disease and congestive failure, together with chamber enlargements found at autopsy is summarized in Table IV.

CARDIOSCOPIC POST-MORTEM CORRELATIONS

1. *Left Auricle* (correlations possible in 54 cases).—Maximal enlargement occurred in four cases and was estimated correctly fluoroscopically in three. The remaining case had been reported as moderately enlarged.

Moderate enlargement was found at autopsy in 21 cases and had been estimated correctly in 19. The remaining two cases had been reported as not enlarged.

No enlargement was found at autopsy in 29 cases and had been reported correctly in each instance.

2. *Left Ventricle* (correlations possible in 65 cases).—Maximum enlargement was found at autopsy in 37 cases and had been estimated correctly in 34 cases. The remaining three cases had all been reported as moderately enlarged.

Moderate enlargement was found at autopsy in 24 cases and had been reported correctly in 22. The remaining two cases had been estimated as maximally enlarged.

No enlargement was found at autopsy in five cases and had been correctly estimated in four. The remaining case had been reported as being moderately enlarged.

3. *Right Auricle* (correlations possible in 39 cases).—Maximal enlargement was present in three cases at autopsy and had been reported correctly in one. The other two cases had been reported as being moderately enlarged.

Moderate enlargement was found in five cases and had been reported correctly in three. The other two cases had been reported as not enlarged.

No enlargement was found in 31 cases and had been reported correctly in 30. The remaining case had been reported as moderately enlarged.

4. *Right Ventricle* (correlations possible in 63 cases).—Maximal enlargement was found in nine cases, seven of which had been correctly reported. The remaining two cases had been reported as moderately enlarged.

Moderate enlargement was found in 32 cases, 22 of which had been reported correctly. The remaining 10 cases had been reported as not enlarged.

No enlargement was found in 22 cases and was correctly reported each time.

The percentage of accuracy of the fluoroscopic estimation of the size of the left auricle was 96, of the left ventricle 92, of the right auricle 87 and of the right ventricle 80. Most of the errors were errors of degree, a finding similar to that in the valvular series.

From these figures one may assume that the accuracy of the determination of the size of the left auricle and left ventricle in nonvalvular heart disease is reliable. The figures on the right auricle are meager, and while conclusions should not be drawn, they seem to indicate that right auricular enlargement may be gauged with a fair degree of accuracy.

The accuracy of the estimation of the size of the right ventricle in this group is not as satisfactory as that for other chambers or for the right ventricle in the valvular group. In reviewing the cases in which mistakes occurred, one is impressed with the fact that all ten errors occurred in cases where moderate enlargement of the right ventricle was reported as no enlargement, and that almost all occurred in patients with left ventricular enlargement (eight with maximal enlargement, two with moderate enlargement).

The reason for the mistaken diagnoses is the same as mentioned in the discussion of similar errors in the valvular group, namely that enlargement of the left ventricle increases the extent to which the left ventricle occupies the left lateral border and diaphragmatic portion of the heart shadow, shortening the second left cardiac arc and protruding into the retrosternal space. The reason the error in right

ventricular estimation was greater in this group is that the incidence of maximal left ventricular enlargement is more frequent than in the valvular group.

CLINICAL-PATHOLOGICAL CORRELATIONS

In reviewing the figures in Table IV it is noted that the cases with hypertension alone and hypertension with coronary artery disease (22 cases) have a lower incidence of right ventricular enlargement than those cases in which cardiac insufficiency had supervened (45 cases). The average thickness of the right ventricular myocardium is greater in the cases with heart failure also. It would seem, then, that the presence of heart failure is one of the important factors in the production of the right ventricular hypertrophy in this series of cases. A corollary to this statement may be that the presence of definite right ventricular enlargement is presumptive evidence for cardiac insufficiency, not necessarily present when the chamber enlargement is first noted.

Left auricular enlargement also was more frequent in cases with heart failure.

The cases with hypertension alone or hypertension with heart failure have heavier left ventricular myocardiums than the cases with hypertension and coronary artery disease. This finding raises the question as to the relationship between cardiac hypertrophy and existent vascular supply.

Aneurysmal dilatation of the left ventricle was found at autopsy in nine cases. A correct diagnosis was made fluoroscopically four times. In four of the cases in which the diagnosis was not made the aneurysm involved the posterior aspect of the left ventricle, and in one case the right ventricle.

Definite murmurs were audible in 41 cases. Of these, a rough systolic apical murmur was heard in 7 cases, a soft apical systolic murmur in 22 cases, a generalized precordial systolic murmur in five cases, and a basal systolic murmur in two cases. A basal systolic and diastolic murmur was heard in five cases.

Definite valvular defects were found at autopsy in 10 cases. Four of these were aortic insufficiency on a luetic basis, one a mitral stenosis, two mitral insufficiency, one mitral stenosis and insufficiency, and one mitral insufficiency with tricuspid insufficiency.

The clinical diagnoses and post-mortem findings were in good agreement so far as the presence of coronary artery disease, cardiac infarction, and heart failure was concerned.

CONCLUSIONS

1. Cardioscopy is a satisfactory procedure for the qualitative estimation of the degree of enlargement of the individual heart chambers.

2. A series of 155 cases of valvular and nonvalvular heart disease is analyzed numerically from the viewpoint of chamber enlargements, valvular defects, ventricular hypertrophy, murmurs, cardiac failure, and the accuracy of clinical diagnoses as compared with autopsy findings.

3. Errors in estimating the size of either ventricle are more frequent when maximal enlargement of the other chamber is present. Certain precautions in avoiding these errors are mentioned.

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THE POSSIBILITY OF EMBOLI FROM ARTERIAL THROMBOSIS SHORT-CIRCUITING PERIPHERAL AND PULMONARY CAPILLARY CIRCULATIONS

REPORT OF A SUGGESTIVE CASE

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FOR years the medical fraternity in dealing with arterial thrombosis has had a sense of security from embolism in such lesions owing to the protection of the capillary network through which presumably emboli could not pass.

Certain unusual features are presented in the case abstracted below which suggest that partial revision of this view may be necessary.

A man sixty-eight years of age who had previously been in excellent health was suddenly seized with an attack of pain on exercise in both feet and legs. His previous vascular condition, as far as could be determined by physical examination, cardiogram, and x-ray, had been excellent and he had played hard tennis within four weeks of the onset of his illness, in itself a fair test of both cardiac reserve and circulation in his legs, though accidents have been known to occur in such conditions without previous symptoms.

His symptoms increased gradually for a month, with progressive disability until the date of his hospital admission on which he showed evidence of thrombosis of the arteries in both lower extremities probably on an arteriosclerotic basis. The lesion was more extensive on the left where the tibial artery was involved than on the right where only the arteries of the foot were affected. The extent of the lesion was demonstrated by the oscillometer and thermometric observations. Within a few days both femoral arteries were also involved. His vascular condition, other than his legs, showed no demonstrable change. Cardiograms had been taken in 1924, 1933, and 1934 and except for lessened amplitude in T_2 , which in August of 1935 was almost isoelectric, were unchanged. These changes are certainly not unusual in a man of his age. The x-ray film of the heart could be superimposed on those taken on many occasions in the past ten years and there was no calcification of the aorta, while the femoral and tibial arteries showed only slight calcification.

His physical examination was negative except for the vascular condition of the legs. The retinal arteries showed no change.

His blood count was as follows: Hemoglobin, 100 per cent; Red blood cells, 4,830,000; White blood cells, 7,500; Polymorphonuclears, 59 per cent; Lymphocytes 38 per cent; Monoeytes, 1 per cent; Basophiles, 1 per cent; Eosinphiles 1 per cent.

Urine was negative.

Thorough examination showed no demonstrable focus of infection, though for some years he had had a slight Vincent's infection of the gums, which was under control at the moment.

Three weeks previous to the onset of his leg symptoms he had had a febrile attack with gastric and abdominal symptoms, lasting a week, of unknown causation.

History, except for the excessive use of tobacco, was excellent.

To save his leg, treatment by the Pavex Boot, with its intermittent negative and positive pressure phases, was instituted, with marked improvement in the local circu-

lation. On September 7 he began to have a little abdominal pain, with right sided costovertebral tenderness, and a little temperature, leucocytosis of 8,000 with 70 per cent polys, which rose on the eighth to 12,000, with 83 per cent of polynuclear cells. There was no pus in the urine.

On September 10 he had a little tingling in the left arm and a little ataxia in the finger to nose test. He was seen by a neurologist who found no sign of central involvement. This, however, went on to a definite left-sided ptosis with very slight speech defect and was followed by tremor and weakness of the left arm, which was obviously central. On the eleventh of September he had a severe attack of upper abdominal distress with nausea and vomiting. In the absence of organic intrinsic lesions of the stomach, gallbladder, or upper intestine, which were ruled out by x-ray examination, we began to think in terms of either extension of his thrombosis to the abdominal vessels or a coronary thrombosis without precordial pain. The latter proved to be the case as shown by the cardiogram of September 12.

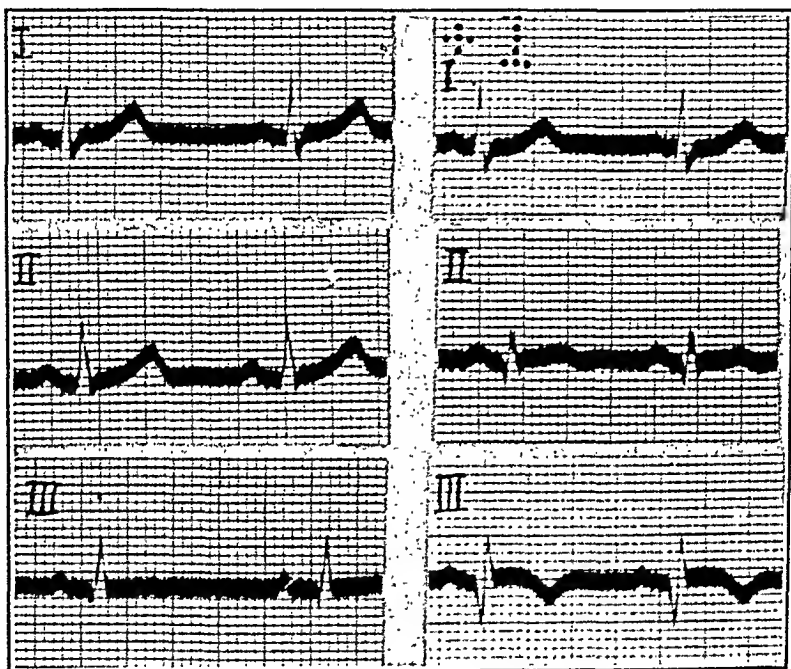


Fig. 1.

Fig. 2.

On September 24 he developed a new focus of clotting, the radial artery in the right arm. The symptoms of this lasted only a few hours.

For years he had had a low rather than high blood pressure, 112/70 and 115/80 in 1934. Blood pressure on admission was 120/62 but rose with the increase of his thrombosis to averages of 160 to 180 systolic and 70 to 90 diastolic, where it had remained until June, 1937.

Four months later, treatment still being continued, he had a second coronary attack. The causation of his initial lesion and of his numerous arterial accidents was puzzling to us. There was no evidence of anaphylaxis or infection. With each coronary occlusion he had a rise in temperature, leucocytes, and sedimentation rate. His uric acid had tended to be high for a number of years; 5.6 mg. per 100 c.c. in 1934; 4.8 mg. per 100 c.c. in 1933. On Sept. 12, 1935, blood urea was 0.36 gm. per liter; blood Nonprotein nitrogen, 0.33 gm. per liter; blood carbon dioxide combining power, 50 per cent. On September 26 blood cholesterol was 208 mg. per 100 c.c. On October 8 showed blood amylase 23.8; October 22, blood urea was 0.38 gm. per liter; blood cholesterol 225 mg. per 100 c.c. and blood uric acid 3.0 mg. per 100 c.c.

However, the tobacco and an unknown infection seemed to be the most reasonable precipitating causes in a man with only very slight demonstrable arterial changes. We could find no evidence of infection elsewhere and were inclined to think of the explanation as slow and generalized endarteritis, though we called the cause X-factor.

The treatment by the boot method was discontinued in the spring of 1936. Since that time he has had no further arterial accidents.

Having noticed in the literature reference to the occurrence of arteriovenous anastomoses, it seemed possible to the author that the alternating negative and positive pressures of the boot might have dislodged thrombi existing in the arterioles or in the Suquet-Hoyer canals. A discussion of the literature on these vessels may be pertinent in a theoretical discussion of the case.

The arteriovenous anastomosis first described by Hoyer¹ in 1877 was considered a very exceptional formation and of importance only in giving rise to the glomus tumor. The universality of its occurrence in the digits of the feet and hands and its functional importance in protecting extremities from cold has been proven by Grant² and by German observers³ and the presence of thrombi in the anastomoses themselves as occurring regularly in thrombo-angiitis obliterans has been demonstrated by Popoff.⁴ We may well pause and consider the possibility of an embolus becoming detached, passing into the veins, the heart, and the lungs. The problem is the probable clinical effect. In this a consideration of the size of the anastomoses is important. Grant gives the diameter as from 18 to 150 microns. Popoff,⁴ however, states that in thrombo-angiitis obliterans abnormal functionless anastomoses are found which are much larger, 100 to 350 microns in diameter. The number of normal anastomoses is given by Grant as 50 to 500 per square centimeter. Except possibly from thrombosis in these abnormal anastomoses a lesion in the lung caused by embolism nonseptic in nature would be difficult if not impossible to detect clinically. The rich pulmonary blood supply would probably prevent increase in size of the small initial lesion. The result, then, of an embolus passing from the periphery into the lungs through arteriovenous anastomoses is probably, from a clinical point of view, relatively unimportant in noninfectious thrombosis. In a septic thrombosis, however, this might well give a clue to the origin of certain unexplained septic lesions in the lung.

Does this, however, complete the picture? The pulmonary capillary system still protects the arterioles of the general system from embolic processes. Are there any means by which the capillaries of the lesser circulation may be short-circuited? Olkon and Joannides⁵ by direct observation demonstrated capillary vessels of two distinct calibers in the network of the capillary bed. Daly comments, "In this observation we have evidence that the blood in a number of the smaller capillaries covering the alveolar surface can be shunted through other channels." MacGregor⁶ also suggests that a vascular shunt exists, in his work with drug

injection into isolated lungs. Wearn's repetition⁷ of Thebesius' experiment⁸ has shown a direct connection other than through the capillaries between the coronary sinus and the heart chambers. "Thebesius introduced his blowpipe into the coronary vein and observed the bubbles escaping into the immersed chambers. In this study the experiments of both Vieussens and Thebesius have been confirmed. Moreover, when perfusion was carried out through the coronary sinus at pressures ranging from 50 to 150 mm. Hg almost all of the perfusate ran out through the Thebesian vessels, and in only a few instances did a few drops escape through the coronary arteries. The result was obtained when saline, acacia, agar, and gelatin were used. Again in these hearts the capillaries were not injected thus showing that the perfusate must have escaped by a more direct and larger communication between the veins and the Thebesian vessels, without having passed through the capillaries." Finally Daly⁹ in his recent Harvey lecture arguing from a teleological viewpoint based on arterial pressure in the lesser and the bronchial circulations, from nerve distribution and nerve stimulation, and from the fact that it is known that blood is not always circulating through the whole of the pulmonary vascular bed, reaches the following alternative conceptions:

First: A conception of a pulmonary vascular bed "in which a number of arteriole capillary vessel networks exist in parallel, so that arteriole constriction of one network diminishes the blood flow in the network it supplies, but shunts the blood through the remainder. This would not be effective in opening up all the alveolar capillaries, which is the desired result during muscular activity."

Second: He next applies the hypothesis of direct arteriovenous anastomoses mentioning that Grant proved in the rabbit's ear their direct control by the sympathetic nervous system and suggests that this hypothesis best conforms to the needs of the body for oxygenation during exercise. "The existence of such a mechanism would largely overcome the difficulties of correlating pulmonary sympathetic vasoconstrictor action with muscular exercise. Under resting conditions a certain number of the communication channels would be open and the alveolar capillary bed which they shunt, closed, whereas during muscular exercise the concomitant stimulation of the pulmonary sympathetic nerves would close the communicating channels and divert the blood through the capillaries, so increasing the vascular bed available for the uptake of oxygen."

Fat embolism, clinically, has been known to pass the peripheral capillaries and pulmonary capillaries and manifest itself in peripheral lesions. (See "Embolism," Nelson Loose-Leaf Living Medicine, Vol. 4, page 590.)

The existence of anastomoses between artery and vein in the lesser circulation would remove the protection of the capillaries of the lesser circulation and an embolus, originating in the arterioles of the foot for

example, might short-circuit both peripheral and pulmonary circulations and cause a lesion in the terminal arterioles of the peripheral circulation.

Would this be clinically manifested? In certain situations this probably can be answered in the affirmative, as in terminal arterioles of the coronary and cerebral arteries for example. The obvious criticism is that such a lesion is too small to be clinically recognized. While true of lesions in most locations it is suggested that even in a microscopic lesion the block of the arteriole and the consequent surrounding edema might be recognizable by electrocardiogram if located in certain of the coronary vessels. Any arteriole block would be followed by a thrombosis in the stagnant blood stream proximal to it, at least as far as the nearest proximal branch and possibly much further, with an ever widening radius of encircling edema. Such a lesion might well cause clinical subjective symptoms as well as certain electrocardiographic changes should the initial lesion be in the coronary arterioles.

The short-circuiting then of the peripheral capillary circulation for small emboli through arteriovenous anastomoses is certainly a physical possibility. The short-circuiting of the pulmonary capillary circulation by the means of these anastomoses is as yet hypothetical. A direct short-circuiting of the entire pulmonary circulation has been proven by the experiments of Thebesius and Wearn.⁸ To offer an open pathway to the actual passing of an embolus through this pathway, however, is dependent upon pressure considerations of which too little is known.

As an alternative suggestion to the generalized endarteritis as a cause for the patient's numerous arterial accidents, I am presenting the possibility of dislodgment of thrombi proven by Popoff⁴ to exist in at least one of the obliterative diseases, thrombo-angiitis obliterans. Such emboli, the dislodgment of which would certainly be aided by the intermittent negative and positive pressure, might, as sketched, short-circuit the peripheral capillaries through the arteriovenous anastomoses and the pulmonary circulation short-circuit the capillaries through the pulmonary arteriovenous anastomoses or the entire pulmonary circulation through the Thebesian vessels.

So far we have shown a possible path based only on physical or mechanical considerations by which emboli dislodged from a peripheral arteriole might short circuit both peripheral and pulmonary circuits and again lodge in the periphery. If, however, the element of infection be considered, the possibilities of passage are increased. Clumps of bacteria or even small particles of a diameter less than two red cells would readily pass the capillaries in both greater and lesser circulations and hence cause the peripheral lesions observed in the above quoted case.

It cannot be denied, however, that a conception of a generalized endarteritis may be the solution of the etiological problem and that the unknown infection from which the patient suffered a month prior to the onset of his symptoms may have resulted in the lesion in his leg and

also in his coronary and cerebral arteries. It is, however, significant that these accidents to the coronary and cerebral arterioles occurred only during the period of treatment with the intermittent pressure boot and that since the discontinuation of this treatment fifteen months ago, he has had no further accidents. It is, therefore, suggested that the dislodgment, by the treatment itself, of emboli which passed through anastomoses of both peripheral and pulmonary circulations, may have caused his numerous arterial accidents. If the infectious idea be accepted, the intermittent pressure might as readily have sent infected particles through the capillary circulations.

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THE DETERMINATION OF EXERCISE TOLERANCE BY THE TWO-STEP TEST*

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THE diagnosis of heart disease involves a consideration of etiology, anatomy, physiology, and the ability of the patient to perform physical exertion. Fairly satisfactory criteria have been established for the interpretation of the anatomical and physiological abnormalities that a patient may present, but many complications are encountered when an estimate of the exercise tolerance or functional capacity is attempted. The reserve power of the myocardium will determine in a large degree the amount of exertion that an individual can accomplish, although there are other factors, such as age, sex, muscular development, coordination, and reflex vascular responses, that affect the exercise tolerance. Furthermore, the ability to perform physical exertion may vary from day to day in the same individual and is influenced by such factors as the general well being, sleep, pain, psychic stress, diet, atmospheric conditions, and probably many others.

To define a standard of accomplishment for any particular group of individuals is obviously difficult, if not impossible, and such a standard must necessarily have a wide range of variation for normal individuals. Practically, it is not difficult to classify patients as to their functional capacity for clinical purposes, if they present obvious signs or convincing symptoms of heart failure while at rest, or on slight exertion. Not infrequently, however, patients in whom no abnormalities are discovered either by physical examination or by other diagnostic methods complain of symptoms suggestive of heart disease. This group is a particularly important one to those practicing medicine in cases where compensation is involved. In the age distribution of patients seen in Veterans' Administration Facilities, arteriosclerotic heart disease without definite physical signs must be considered and distinguished from the so-called functional heart disease and other noneardiac illnesses. Any method that will aid in demonstrating the presence or absence of myocardial or coronary insufficiency is therefore highly desirable.

Many tests have been proposed for estimating the exercise tolerance or functional capacity depending upon some strain, such as the physical

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effort of riding a bicycle to produce abnormal physiological responses characteristic of heart failure. Since these phenomena vary considerably, the criteria have been unsatisfactory and many of the tests are technically difficult and, therefore, limited in their practical usefulness. It has long been known that the blood pressure and pulse rate increase during work, but it has not been determined satisfactorily whether the blood pressure responses, which occur during exercise, are due to the increased output of the heart or to increased peripheral resistance. Wiggers¹ has demonstrated the type of blood pressure and pulse rate changes usually seen during exercise, by means of a circulatory schema, in which the heart rate and systolic discharge are increased and the peripheral resistance then lowered. In the human subject, however, the regulation of blood pressure is complicated by psychic reactions, reflexes from the sino-aortic region, hormonal constrictor and dilator substances, and probably a different response in various parts of the vascular system at the same time.

Many attempts have been made to obtain a measure of the functional capacity of the heart by observing the blood pressure and pulse rate before and after various types of exercise. Of the many modifications that have been proposed, the one described by Master and Oppenheimer² and by Master³ appears to have certain advantages for routine determination of the exercise in ambulatory patients. The apparatus required is simple and easily available; the exercise is one that most individuals are accustomed to, without training; the amount of work performed can be roughly measured and tables of standard exercises, which take into consideration the age, sex, and weight of the individual, are available.

In the Master test the resting blood pressure and pulse rate are compared with the values for these phenomena two minutes after completing the exercise, which consists of repeated ascents on two steps, each nine inches high, a standard number of times in one and one-half minutes. If the levels for the blood pressure and pulse rate do not differ from the resting level, by more than ten points, the patient is considered to have a normal exercise tolerance. It is proposed to report our experience with the use of this test clinically and in addition some observations on the specificity of the criteria.

METHOD

One hundred patients were examined who presented symptoms suggestive of heart disease, the presence of which was subsequently confirmed in some cases by objective evidence, while in a larger group no definite signs of heart disease could be found. Some of the latter group were suffering from conditions that might influence the general tolerance to exercise.

In all cases a complete medical history was taken and a physical examination performed, after which the patient was allowed to lie on the examining table without being disturbed for at least thirty minutes, until the blood pressure and pulse rate seemed to be constant. Blood pressures were taken on the left arm using the auscultatory method and a mercury manometer. Diastolic pressure was read at the point where the sounds became very faint just before completely disappearing. On subsequent tests the preliminary history and physical examination were not repeated and no patient was tested who presented obvious signs of failure. Several patients were examined whose chief complaint suggested the anginal syndrome, but the exercise, required of them for a routine examination, did not precipitate any typical attack of pain.

The pressor reflex, according to the technique of Hines and Brown,⁴ the vital capacity, an electrocardiogram, and x-ray film of the heart, were also obtained in most cases.

The results of the exercise tolerance test were not conclusive for 13 of the 100 cases, because in 12, the number of ascents on the steps was not standard, although the blood pressure and pulse were within normal limits at the end of two minutes and in one, the exercise was standard, but the pulse rate was high, due to many premature contractions. It was not possible to do more than one test on any of these subjects.

Two patients discontinued the exercise because of severe breathlessness although their blood pressure and pulse rate were not elevated. One of these had a tracheotomy, which presumably reduced his ventilation, and the other had a possible pericardial effusion which was never established as the true diagnosis.

Four discontinued the exercise because of weakness and giddiness after doing from 63 to 87 per cent of the standard exercise. In all cases the blood pressures and pulse rates were normal.

When patients complained of severe symptoms, they were usually allowed to do the first test at a rate that was comfortable for them, and as a result, the exercise was not standard in 15 other cases. In this latter group, however, there was evidence of diminished tolerance in the blood pressure or pulse rate, in spite of the substandard exercise.

CONSTANCY OF RESULTS

The exercise test was performed two or more times on 30 patients, and in 19 there was agreement in the tests performed on separate days; that is, the blood pressure and pulse rate were either within ten points of the resting level on both days, or exceeded ten points on both days; in ten cases they were within normal limits on both tests, and in nine cases they were interpreted as showing diminished tolerance in both tests. In the latter group, one patient with hypertensive heart disease showed dimin-

ished tolerance in three tests and after hospitalization for several weeks had a normal tolerance, although the blood pressure continued high. Two patients were examined a year after the first test and their reactions were practically identical in both tests.

In four patients, the systolic blood pressure remained elevated at the end of two minutes in the first test, but on the second examination the blood pressure and pulse rate were normal. One patient had mild hypertensive heart disease and the second examination was made four days later when he stated that he felt better. In one other instance, the examinations were six days apart, while the other two were examined on successive days and their reactions on the first day were only slightly below normal. These four patients were listed among those with normal exercise tolerance for the general tabulation. It is impossible to say what part hospital rest and relief of emotional tension played in changing the response; however, they are likely factors, as Master³ reports that variation in the general well-being due to loss of sleep, excessive smoking, and various drugs such as the barbiturates, caused a reduction of tolerance in his normal series. Three of these four patients were given diagnoses of neurocirculatory asthenia.

In the remaining seven patients the two examinations were not comparable for various reasons. The exercise was not the same on both examinations in three cases; the blood pressure response being normal when less exertion was performed and excessive when more exertion was done; and obvious psychic disturbance in the other four patients prevented the development of proper basic conditions before or after the exercise in at least one of the tests.

It is apparent that uncontrollable factors, such as emotional instability, may cause blood pressure and pulse rate changes, indicating a decreased tolerance, which cannot be confirmed by other tests or other clinical methods. Although the results of this method of testing exercise tolerance were consistent in the majority of cases, the inconsistent results cast doubt on the interpretation of responses indicating decreased tolerance.

TYPES OF REACTION

Master³ and Nylin⁵ refer to the reports in the literature of observations showing the tendency for the systolic pressure to be elevated after exercise, while the diastolic pressure and pulse rate exhibit little variation.

The usual reaction in the 132 tests in our series was a moderate elevation of the systolic blood pressure above the resting level, two minutes after completing the exercise, with slight changes in the diastolic pressure and pulse rate above or below the resting level. In 52 instances the systolic pressure was more than 10 mm. of Hg above the resting level, which corresponded to similar excessive rises in diastolic pressure in only four cases and pulse rate increases of more than 10 beats per mm.

in twelve patients. Only three patients exhibited a significant increase of pulse rate who did not show a comparable elevation of the systolic pressure.

A considerable proportion of all the patients showed only a decrease in the diastolic pressure after exercise, perhaps because of failure to get a basic level during rest, while the systolic pressure was below the resting level two minutes after exercise in only 17 tests. Three patients exhibited a decrease of systolic pressure of more than 10 mm. of Hg. This could not be explained on the basis of observed changes in the cardiac mechanism, although they all presented marked circulatory symptoms and particularly asthenia. It was not possible to reproduce similar symptoms by stimulation of the vagus through the carotid sinus reflex and it was inferred that a peripheral mechanism was responsible for the failure to maintain the level of systolic pressure in these patients.

The pulse rate, counted by manual palpation of the radial artery, was below the resting level in approximately 25 per cent of all the tests. The decrease was more than 10 beats per minute in only three patients, two of whom had resting levels above 100 beats per minute. Bierring, Larsen, and Nielsen⁶ state that they have never seen the pulse curve, after exercise, fall below the resting pulse in normal persons, and have seen it only infrequently in cardiac patients. These authors recorded the heart rate electrocardiographically, while in our series the decrease in pulse rate, after exercise, was observed by a less accurate method, and no particular significance was attached to it.

RELATION TO THE PRESSOR REFLEX

Since the systolic elevation of the blood pressure was the principal criterion for determining diminution of the exercise tolerance by the Master test, as indicated in the previous section, it was desirable to examine the reaction of the blood pressure to other stimuli than exercise.

Hines and Brown⁴ proposed the cold pressor test which, they believe, indicates "the potential reactivity of the vasomotor nervous system and that hyperreactions are synonymous with potential or existent hypertension, whether the levels of the blood pressure are increased or not." Assuming this to be true, a hyperreaction which is defined as a minimal increase in the systolic blood pressure of 26 mm. of Hg, or of the diastolic pressure of 22 mm. of Hg might also be reflected in the blood pressure reaction to exercise. The number of patients with hypertension in any group will affect the number showing a hyperreaction to cold, as a high percentage of patients with elevated blood pressure give an excessive reaction to the cold stimulus, according to Hines and Brown. This was demonstrated when the patients were classified according to the presence or absence of definite evidence of heart disease or hypertension. The heart disease group contained 61 per cent of hyperreac-

tors to the cold test, while the group without definite heart disease or hypertension contained only 39 per cent hyperreactors. Dividing the patients on the basis of their response to the step test, patients with hypertension appeared in both the normal and diminished groups but principally in the latter. The percentage of patients showing hyperreaction to the cold test was 35 per cent in the normal exercise tolerance group and 55 per cent in the diminished tolerance group.

In order to avoid an arbitrary division into groups, 83 patients were chosen who had completed both the pressor reflex and exercise tolerance tests on the same day. A correlation was run between the maximum systolic blood pressure elevation during the cold stimulus, and the elevation of the systolic blood pressure two minutes after exercise. The coefficient of the correlation derived was +9 out of a possible 100 for a perfect correlation, which expresses a very low grade relationship. On the basis of this comparison, the blood pressure and pulse rate responses to exercise were not apparently related in any important degree to the "potential reactivity of the vasomotor nervous system" as shown by the cold pressor test, and might, with more assurance, be considered an evidence of response to factors outside the vasomotor system.

RELATION TO THE LILJESTRAND-ZANDER PRODUCT

Nylin⁵ refers to the reports of Liljestrand and Zander who observed a linear relationship between the product of the "reduced amplitude" (ratio of pulse pressure over mean blood pressure) multiplied by the pulse rate, and the minute volume of the heart. In Nylin's report he showed that the Liljestrand-Zander product was retarded in its return to normal in heart patients with decompensation although the values for normal and decompensated individuals overlapped.

We calculated the Liljestrand-Zander product from our data for the blood pressures and pulse rates at rest and two minutes after completing the exercise, expressing the difference as a plus or minus percentage of the product of the values at rest. In our series, the average difference was +16.8 per cent (standard deviation 17.20) in the patients with normal tolerance, according to the step test, and +35 per cent (standard deviation 22.88) in the patients with diminished tolerances. The range of the percentage differences between the products at rest and after exercise was from +57 per cent to -13 per cent in the normal tolerance group and from +82 per cent to -19 per cent in the diminished tolerance group. Because of the large standard deviations, the differences in the two groups were not significant and would not indicate any correlation between the interpretation of the step test and the Liljestrand-Zander product. Our observations were not sufficiently prolonged to determine the time required for the product to return to normal values.

If the Liljestrand-Zander product has a linear relationship to the minute output of the heart, our data would indicate that the minute volume might be increased or decreased after exercise in both normal individuals and patients with heart disease, with a tendency for a greater increase in the latter group. Similarly, the values for the actual product varied widely and were often highest for those who presented the most evidence of heart disease. Starr, Collins, and Wood,⁷ reported "certain patients with advanced myocardial disease have larger cardiac outputs than some normal persons" and concluded "these values throw very little light on the condition of the heart." Harrison⁸ summarized the results of various investigations of the cardiac output in heart failure, stating "no parallelism exists between the severity of the symptoms and the level of the cardiac output."

Assuming, therefore, that the Liljestrand-Zander product does have a close relationship to the minute volume of the heart, the absence of significant correlation between the interpretation of the step test and either the product or the percentile change of the product after exercise, does not necessarily invalidate the step test as a method of determining functional capacity of the heart.

RELATION TO VITAL CAPACITY

The vital capacity was determined for 81 of the 87 patients for whom there was an exercise tolerance test that could be interpreted, and this was compared with the calculated theoretical capacity, based upon 2,500 c.c. per square meter of body surface as proposed by West⁹ for normal individuals. It is well recognized that many factors besides pulmonary congestion due to heart disease will affect the vital capacity and that there is considerable variation among normal subjects, although the vital capacity for the same normal individual is quite constant.

The vital capacity of the patients with definite heart disease without any signs of failure varied from 50 per cent to 101 per cent of their calculated normals, while the vital capacity in the group without definite evidence of heart disease ranged from 55 per cent to 112 per cent of the calculated normal; the average for the two groups was 76 per cent and 83 per cent, respectively.

When compared with the results of the step test, regardless of the presence or absence of signs of heart disease, the patient with a normal tolerance had an average vital capacity of 82.5 per cent of the calculated normal and those with a diminished tolerance, an average of 78.3 per cent. Statistically this was not a significant difference. A frequency curve showed the peak of incidence at about 70 per cent of the theoretical normal capacity for both groups; the group with diminished tolerance had more cases below 60 per cent, while the group with normal tolerance had a greater number with 100 per cent or more of the calculated vital capacity.

In 20 patients the vital capacity was measured before and immediately after exercise. In all but one case, the latter reading was less than the first, the average reduction being 368 c.e. or about 10 per cent of the resting capacity. Levine and Wilson¹⁰ reported only a 2-per cent reduction in normals exercised to breathlessness. As a rule the vital capacity was reduced less than 10 per cent and in some in which respiratory distress seemed most prominent, the percentage reduction was the least; thus it did not seem possible to correlate observed breathlessness with reduction in the vital capacity. Levine and Wilson¹⁰ reported in patients with "irritable heart" that the breathlessness was out of proportion to the vital capacity, while the difference between mild and severe cases was not great. Arnett and De Orsay¹¹ and others have pointed out the variability of the vital capacity, and emphasized that the value of the examination is largely in comparing measurements, from time to time, on the same individual.

In our series, there was very little correlation between the vital capacity and definite signs of heart disease. On the basis of West's formula for normal men, Arnett¹² concludes that an absolute reduction of 1,644 c.e. from the calculated theoretical capacity is significant, being three times the standard deviation. Only 18 of our patients showed this amount of absolute reduction, some only after exercise, while several patients with severe heart disease, including two who died within a year with heart failure, did not show this much reduction. It appeared, therefore, that, as an isolated examination, the vital capacity did not correspond closely either to the tolerance to exercise, as estimated from the history and the step test, or to the evidence of heart disease in patients without definite failure.

RELATION TO DIAGNOSIS

The final consideration, in determining the usefulness of the two-step test for estimating exercise tolerance, was to compare the interpretation of the test with other clinical manifestations. For this purpose the patients were classified in four groups on the basis of their response to the step test and the presence or absence of definite evidence of heart disease. The groups were as follows: (1) diminished exercise tolerance without heart disease; (2) diminished exercise tolerance with heart disease; (3) normal exercise tolerance without heart disease; (4) normal exercise tolerance with heart disease. The first and last classifications presented the principal inconsistencies between the clinical signs and the results of the step test and will be discussed in most detail. It should be noted that, on the basis of history, practically all of these patients could be said to have had some impairment of functional capacity, although in many instances the physical examination did not reveal sufficient cause, either in the heart or other systems, to account for the disability.

In the group with diminished tolerance and without definite evidence of organic disease of the heart, there were 19 men with an average age of forty-five years, ranging from thirty-eight to fifty-seven years. All of these patients complained of symptoms suggesting circulatory dysfunction, and some had been told that they had heart disease. Breathlessness, on exertion, was one of the most common complaints, but fatigability and precordial pain were more often causes for disability. In several cases the principal problem was to determine whether thoracic pain was significant of the anginal syndrome. Five patients gave a history of repeated attacks of unconsciousness and two had suffered from convulsive seizures, of unknown cause, for many years. Several were chronic alcoholics; one had had a recent attack of acute cholecystitis; one had severe diabetes which was not properly stabilized; and one had had a recent postoperative respiratory complication. In addition to these illnesses, two patients presented the manifestations characteristic of severe neurocirculatory asthenia, and an associated "nervousness" or other psychoneurotic complaints were the rule rather than the exception throughout the group. At least nine of the 19 patients claimed that the onset of their symptoms occurred during their military service, about eighteen years previously, and most of these men had done very little work, because of their symptoms, since discharge from the service.

None of the patients in this group exhibited enlargement of the heart on physical examination and the teleroentgenograms showed no unusual configurations. The blood pressure was not consistently elevated in any of the patients; the highest systolic pressure was 158 mm. of Hg and the highest diastolic pressure was 90 mm. of Hg. There was no evidence of involvement of the heart valves in any patient.

Electrocardiograms were obtained for all patients in this group and were normal, with five exceptions. In one tracing, the voltage of the QRS complexes was 0.5 millivolt or less in all three leads, in another the heart rate exceeded 100 beats per minute, and in a third tracing the voltage of the T-waves in Lead I was less than 0.1 millivolt. An electrocardiogram was obtained on one patient, shortly after a fainting attack, which showed slight depression of the R-ST intervals, as compared with previous tracings. In the fifth patient a record was obtained during an attack of paroxysmal auricular fibrillation; however, on the following day after the cessation of the attack, an electrocardiogram was obtained which showed no abnormality. Changes, of the type enumerated above, have been described as occurring in patients with no apparent heart disease.

It could not be definitely determined whether some of the patients in this group had coronary arteriosclerosis with myocardial impairment, and whether the patient with paroxysmal auricular fibrillation had organic heart disease, but it was the clinical opinion, based on other

methods of examination, that the symptoms which were presented were not due to organic heart disease. If this was true, it would appear that the blood pressure and pulse rate responses to exercise may be exaggerated in the absence of organic disease of the heart when there is disease or dysfunction in other systems. Less than a year has elapsed since most of these patients were examined by the two-step test and subsequent events may indicate that greater specificity for the test might have been assumed.

There were also in our series, 15 patients who had definite signs of heart disease or hypertension who gave a normal response to the step test. The patients with resting blood pressures above 150 systolic and 90 diastolic were included in this group, whether cardiac enlargement or myocardial damage was demonstrable or not, although only two of the nine hypertensive patients showed any suggestive changes in the electrocardiograms. Of the remaining six patients, two had rheumatic heart disease, with mitral stenosis; one had congenital patent ductus arteriosus; and one showed a short auriculoventricular conduction time, with prolonged intraventricular conduction time, and a history of paroxysmal tachycardia. In this patient the lesion might have been a congenital abnormality and not necessarily disabling, except during the paroxysms of tachycardia. One patient was considered to have arteriosclerotic heart disease largely on the basis of a history of an acute coronary occlusion two years previously, although a small downward deflection (Q) in Lead IV was the only residual evidence of myocardial damage. Another patient was given a diagnosis of probable arteriosclerotic heart disease, on the basis of a history of pain on effort and low voltage T-waves in all leads. This patient's threshold for pain production must have been high because he did not develop pain while completing a test with twice the number of ascents standard for his age and weight.

It was conspicuous that the cardiac involvement in these patients when present was not severe and was not incompatible with a good exercise tolerance, indicating good myocardial reserve. They would have been grouped clinically in Classes I and IIA according to the American Heart Association rating of functional capacity.

Twenty-one patients were considered to have both a diminished exercise tolerance and heart disease, although in three patients, with the exception of slight hypertension, there was very little on which to base a diagnosis of heart disease. In general, the cardiac involvement exhibited was definite and was more severe in these patients than in those in the previous group. The electrocardiographic changes in 11 instances indicated myocardial damage, the average age was slightly higher (forty-eight years) and more patients were considered to have arteriosclerotic heart disease; but in some instances the cardiac reserve, estimated clinically from the history, was not less than in patients in which the step

test was within normal limits. At the time of the examination none of the patients had any signs of congestive failure, although one has subsequently progressed to this state, and one died following surgical treatment of a carcinoma of the rectum.

The largest group contained 32 patients who showed a normal response to the step test and had no definite evidence of heart disease. Two of these patients showed occasional premature contractions in the electrocardiogram; the voltage of the QRS complexes was low in two cases; two showed sinus tachycardia; and one a deep Q_3 . In the absence of other changes it was considered that these deviations were not evidences of myocardial change. As in the other groups some of these patients complained of fatigue, dyspnea, palpitation, fainting, and pain in the chest. The exercise test was most in accord with the clinical findings in this group, as it supported the opinion that no organic disease of the heart was present when objective signs were not discovered upon which to base a diagnosis. Most of these patients appeared to belong to the psychoneurotic classification and diagnoses of neurocirculatory asthenia had been carried, in some instances, for many years.

HEART PAIN

Several of the patients in this series complained of precordial pain, which was not usually typical of significant heart pain, although the differentiation, entirely on history, was not satisfactory. These patients were given a standard test and if pain did not develop, they were instructed, at a subsequent examination, to make as many ascents as possible or until pain developed. In some cases such a procedure caused pain after a comparatively few ascents, but when the patient complained of general fatigue, without developing heart pain, the history of thoracic discomfort was largely discounted as evidence of serious coronary artery disease.

COMMENT

It is apparent from the preceding discussion that a decrease in the exercise tolerance, as manifested in the step test, was not considered to be an infallible evidence of heart disease, because various extracardiac factors, such as infections or abnormal mental states, with autonomic nervous system imbalance, might be responsible for the character of the blood pressure and pulse rate responses.

In this group of patients who complained of symptoms under slight to normal activity there was generally fair agreement between the results of the test, the extent of the cardiac involvement found on examination, and the estimation of the functional capacity from the history. In some instances, however, the diminished tolerance observed by the test was definitely inconsistent with the results obtained in other cases, judging

by the patients' statements as to their habitual activity and the degree of cardiac involvement. It does not seem warranted, therefore, to place much value upon this test as a dependable measure of decreased cardiac functional capacity.

Since the exercise was mild, it was not thought incongruous that some patients with organic disease of the heart should have a normal exercise tolerance by this test, indicating a fairly good cardiac reserve. Unless a maximum strain is imposed upon the heart, however, the earliest stages of heart failure cannot be differentiated, and the response of the patient with organic damage may be as good as that of the normal individual to milder exercise. For this reason normal exercise tolerance by the two-step test cannot safely be interpreted as indicating that no reduction in the functional capacity of the heart exists. On the other hand, no patient, who was judged clinically to have more than moderately reduced functional capacity, gave a normal response to the test.

With these limitations in mind, the test provides a means of examining a patient's response to exercise under reasonably standard conditions, but the interpretation of the test should not be given any decisive importance.

CONCLUSIONS

The test was easily performed and did not require complicated apparatus or much cooperation on the part of the patient.

The results were occasionally difficult to interpret and did not always agree on successive days when the same patient was tested.

The usual response, two minutes after completion of the exercise, was an elevation of the systolic blood pressure which appeared to be unrelated to the level of the resting blood pressure or the response to a cold water stimulus.

The relation of the sustained rise in the systolic blood pressure to the condition of the heart could not be directly demonstrated, and in the absence of definite organic disease of the heart, other conditions such as infections and psychoneuroses were associated with reactions characteristic of diminished exercise tolerance.

A diagnosis of heart disease is not warranted, based on the results of the two-step test alone.

A single test is not dependable evidence of reduced functional capacity and repeated tests that agree should be given only suggestive value.

The earliest stages of heart failure cannot be differentiated by the test, although normal responses are more dependable and indicate normal or only slightly reduced functional capacity.

A modification of the test is a useful method of studying patients who complain of thoracic pain.

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Department of Clinical Reports

TRANSIENT, RECURRENT, COMPLETE LEFT BUNDLE-BRANCH BLOCK

REPORT OF A CASE

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IN ALL probability transient, complete bundle-branch block is not a rare condition. Nevertheless, there have been very few recorded observations of this condition.

CASE REPORT

The patient, a man, aged sixty-eight years, first came to me on April 1, 1928, complaining of slight palpitation after playing eighteen holes of golf, and with this a feeling as though his heart were irregular. This was his chief complaint and only

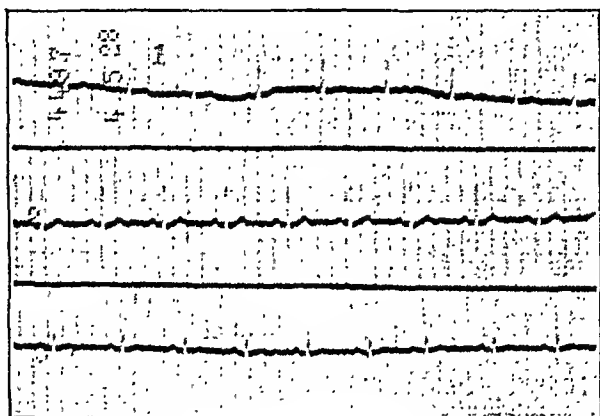


Fig. 1.—Electrocardiogram (4497)A. April 5, 1928. Slight palpitation after eighteen holes of golf. No evidence of intraventricular conduction. P-R, 0.16; QRS, 0.06.

occurred following prolonged exercise. Two years before I saw him he had had a bilateral herniorrhaphy, with an uneventful postoperative course. Remainder of past history and family history were noncontributory and irrelevant.

On physical examination he appeared a robust, well-preserved elderly man lying perfectly flat on the table without discomfort. He had a fairly marked coarse tremor of both hands and evidence of generalized arteriosclerosis. His heart was not enlarged, rate was moderate, with regular sinus rhythm; there was a slightly rough short systolic murmur at the base. The remainder of the physical examination was essentially negative. Likewise on fluoroscopy the heart presented an average silhouette, except for slight widening of the aortic arch shadow.

Laboratory Findings.—The blood Wassermann reaction was negative. Red blood cells numbered 5,100,000, and the hemoglobin was 108 per cent. The urine showed

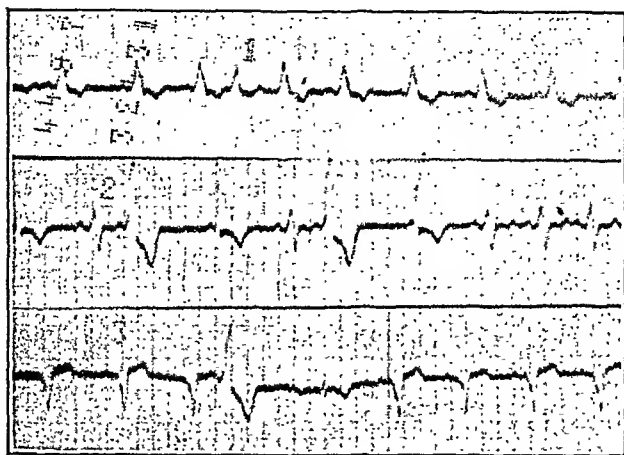


Fig. 2.—Electrocardiogram (4497)B. March 24, 1931. Patient having occasional attacks of palpitation. Complete left bundle-branch block. Numerous auricular and ventricular extrasystoles from different foci. P-R, 0.16; QRS, 0.16.

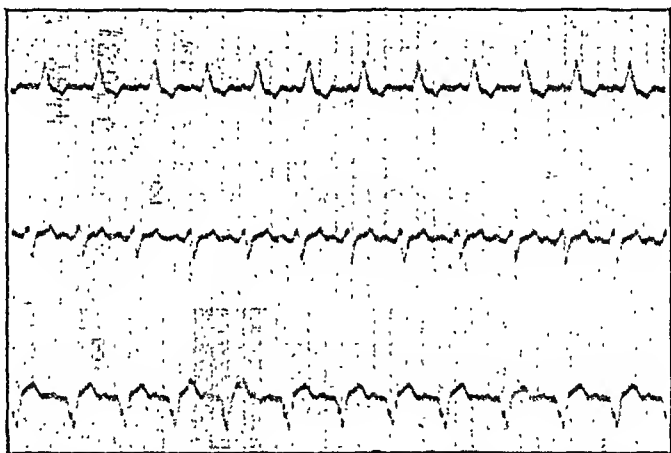


Fig. 3.—Electrocardiogram (4497)C. Sept. 10, 1931. Patient playing nine holes of golf twice a week. Asymptomatic. Complete left bundle-branch block. P-R, 0.16; QRS, 0.16.

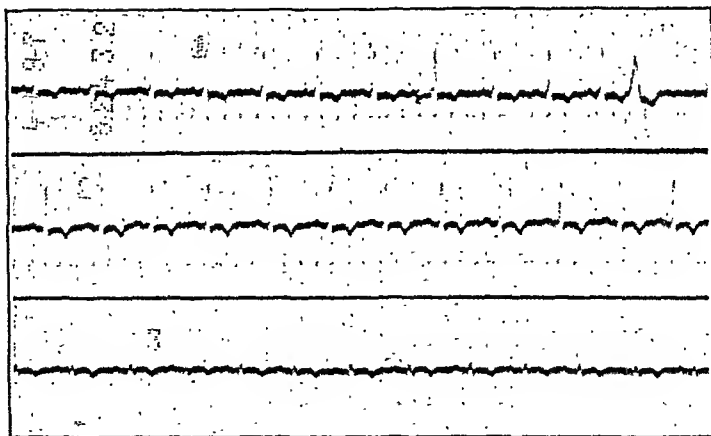


Fig. 4.—Electrocardiogram (4497)D. June 24, 1932. Asymptomatic. No conduction defect. T-waves negative in all three leads. One ventricular extrasystole. P-R, 0.16; QRS, 0.06.

a faint trace of albumin, which was not always present in subsequent specimens. Nonprotein nitrogen was fairly constant and was around 42 mg. per 100 c.c. throughout nine years of observation.

Clinical Course and Electrocardiograms.—Ten electrocardiograms were taken from first office visit in April, 1928, through the most recent examination in February, 1937. The first tracing (Fig. 1) showed no significant findings. The second (Fig. 2) in March, 1931, three years later, revealed a complete left bundle-branch block. Several weeks prior to this he had had an automobile accident without serious injury, but following this he had had palpitation frequently. In September, 1931, six months later, the bundle-branch block was still present (Fig. 3) and in addition, T_2 had changed from negative to positive. At this time he was relatively asymptomatic and

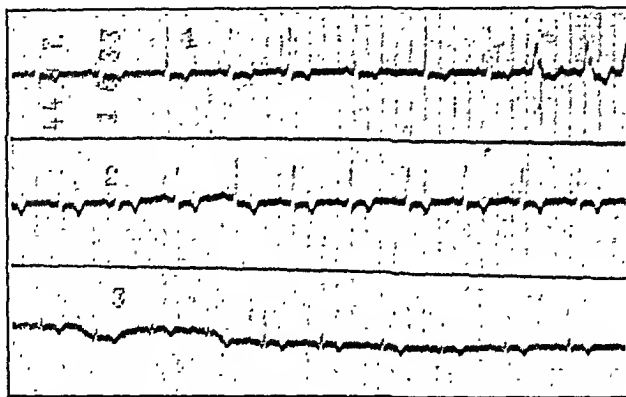


Fig. 5.—Electrocardiogram (4497)E. Jan. 6, 1933. Continues asymptomatic. Note last three complexes in Lead I. P-R, 0.16; QRS, 0.06. P-waves present. QRS, 0.16.



Fig. 6.—October, 1934(G). April, 1935(H). March, 1936(I). February, 1937(J). Electrocardiogram (4497) October, 1934, to February, 1937. No cardiac symptoms. Permanent left bundle-branch block.

was playing nine holes of golf a day. When next seen on June 24, 1932, nine months later, his block had disappeared, and T_2 had changed back from positive to negative (Fig. 4). This was the first available evidence of the transient nature of this block, and at the time of his visit in January, 1933, eight months later, quite by accident an interesting demonstration of this was obtained. The electrocardiogram (Fig. 5) caught three complexes in Lead I, showing bundle-branch block, while the remainder of the tracing was normal, except for T-wave negativity in all three leads. Nine months later a left bundle-branch block was present in all three leads (Fig. 6), and this persisted throughout four subsequent tracings taken at approximately yearly intervals. Throughout this entire period the patient has con-

tinued to live an active life mentally and physically and, except for a little palpitation occasionally, a little dyspnea on moderately severe exertion, and recently a few dizzy spells, he has been symptom-free.

DISCUSSION

Conduction bundle-branch block defects are generally considered manifestations of severe myocardial damage, and when present usually remain as a fixed condition throughout life. Few exceptions to this observation have been recorded. This applies only to bundle-branch block as a manifestation of organic heart disease and does not include the so-called functional bundle-branch block described by Sigler,¹ or those cases of bundle-branch block with short P-R interval in healthy individuals recorded by Wolff, Parkinson and White,² and since described by many others. Nor does it include those transient episodes of impaired conduction of the bundle induced by the combined administration of digitalis and quinidine.

Attention has been called recently to the infrequency or recurrent bundle-branch block by Willius and Anderson,³ who added one case to the six previously described in the literature; of these seven cases four were examples of complete and three of incomplete bundle-branch block. Willius and Anderson³ point out that in all the six cases previously described in the literature the episodes of conduction bundle defect were associated with periods of cardiac insufficiency; in one they were related to attacks of paroxysmal auricular fibrillation; in the others they were associated either with attacks of pulmonary edema or with other manifestations of decompensation and disappeared when compensation was restored. The case of Willius and Anderson³ was of particular interest because of the complete absence of cardiac symptoms at any time in spite of the complete bundle-branch block as well as prolonged A-V conduction-evidence of fairly profound interference in impulse conductivity.

SUMMARY

A case of transient recurrent complete left bundle-branch block followed over a period of nine years with electrocardiograms is reported, and the meager literature is briefly reviewed.

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DISSECTING ANEURYSM OF THE AORTA: ANTE-MORTEM DIAGNOSIS AND COURSE FOR FIFTY-THREE DAYS*

CASE REPORT

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THE clinical diagnosis of dissecting aneurysm of the aorta has been made with increasing frequency in the past two or three years. Yet the number of cases reported is few and the following typical case is

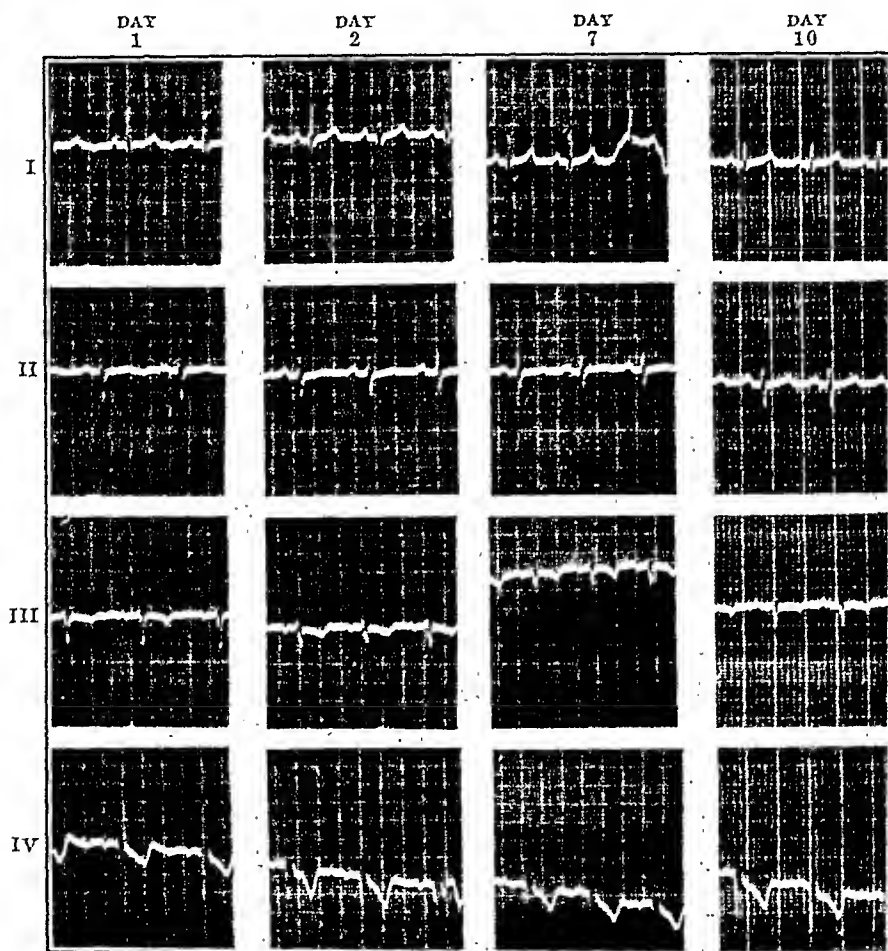


Fig. 1.—Serial electrocardiograms taken on the first, second, seventh and tenth days of illness. There is no evidence of coronary occlusion.

reported in an attempt to continue the interest that has been stimulated. The observations on this patient cover a period of fifty-three days.

CASE REPORT

The patient, T.S., was a forty-five-year-old colored male janitor admitted to Grady Hospital April 20, 1937, with the complaint of severe abdominal pain.

*From the Department of Medicine, Emory University School of Medicine.

Past History.—His past history contained few important items. Nine years previously he had been treated for an inguinal adenitis associated with recurrent gonorrhea. No Wassermann test of the blood was reported and no estimation of his blood pressure was made.

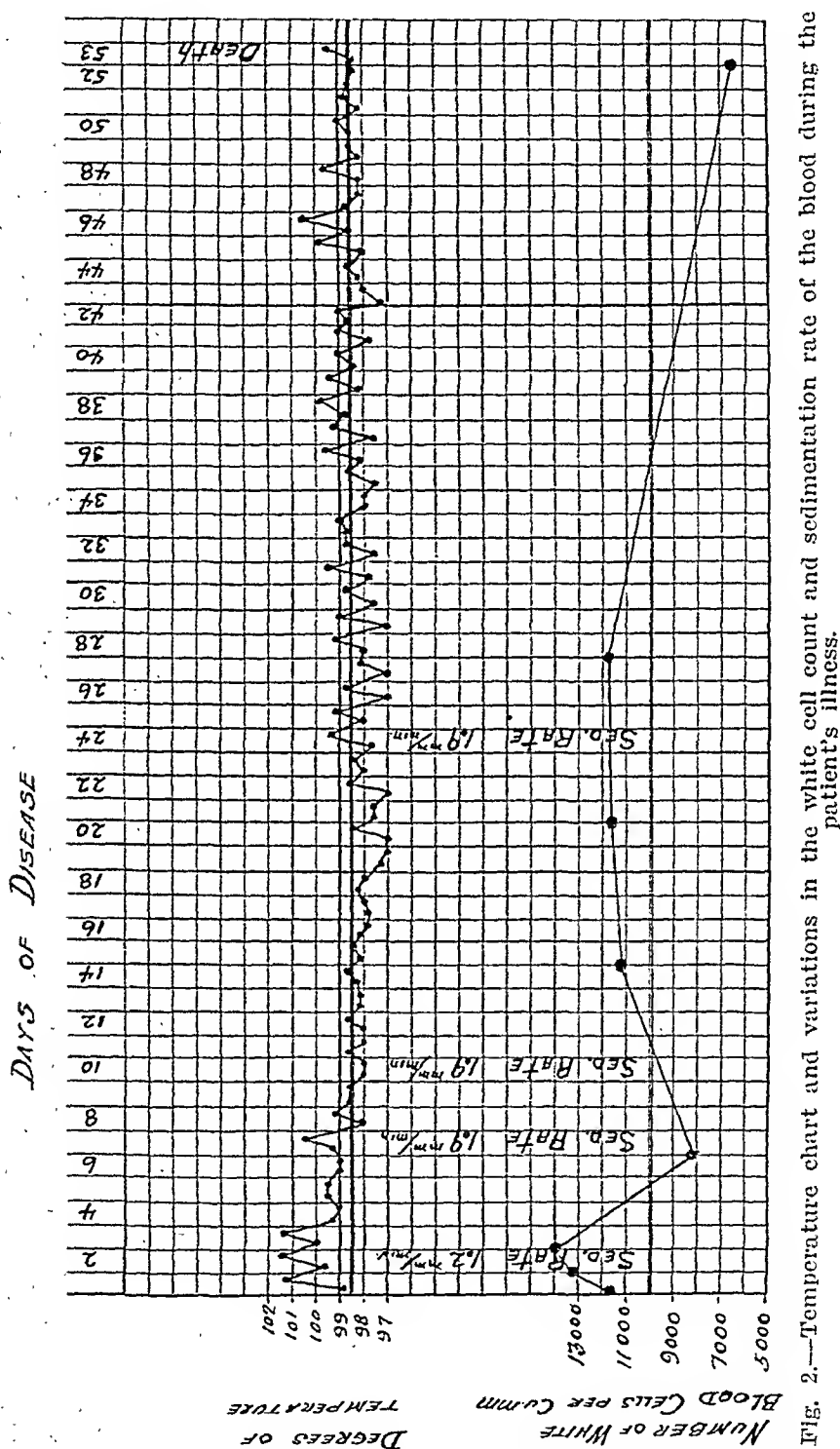


Fig. 2.—Temperature chart and variations in the white cell count and sedimentation rate of the blood during the patient's illness.

Three years prior to his present admission he had a penile sore diagnosed as primary syphilis. He stated that a Wassermann test on his blood was positive at that time and that he received 16 injections for syphilis. During and since that time the patient had worked regularly as a janitor and had had no complaints.

Present Illness.—His present illness began at 1:00 A.M. on April 20, 1937, at which time he was awakened with a severe pain under the lower angle of the left scapula. The pain was sharp and constant and at first did not radiate. It was not described

as "tearing" by the patient. The pain was so severe that he was taken to the emergency clinic where he was given one-fourth of a grain of morphine and returned home. His pain was not lessened. About two hours after the onset, the pain began to move around to the left flank and to the abdomen about the navel. It remained constant and exerceiating in character. There was some nausea but no vomiting. The patient had "cold sweats," but he did not have a "fear of impending death." Seven or eight hours after the pain began it became slightly less severe and at this time the patient was seen in the medical clinic.

Examination.—He was a muscular colored man, obviously suffering from pain. His face was drawn and he groaned considerably. He was more comfortable bending slightly forward than in other positions. There was engorgement of the neck veins, reaching on the left to the lobule of the ear and on the right only one-fourth of this

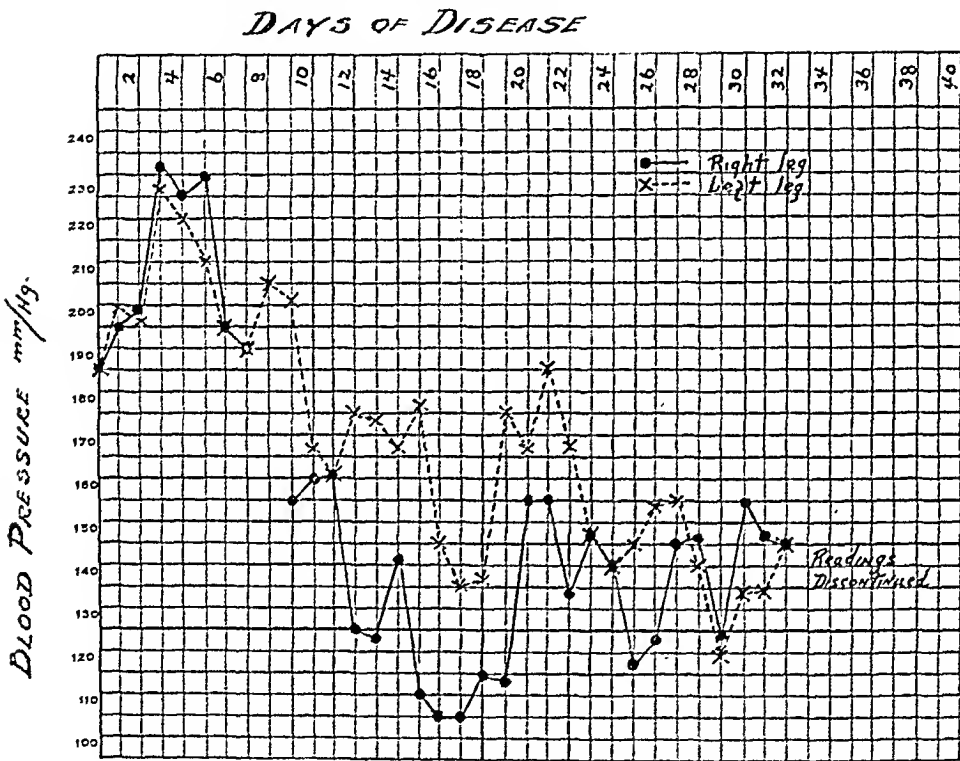


Fig. 2.—Comparison of the systolic blood pressure in the right leg and in the left leg during the first thirty-two days of patient's illness.

distance. The patient's temperature was 98.4° F., his respirations numbered 30 per minute, his pulse 80 beats per minute. The pupils of his eyes were equal on the two sides. On examination of the ocular fundi, a well-advanced sclerosis of the arteries was found; there were no hemorrhages. Examination of the lungs revealed no abnormal findings. There were no abnormal pulsations about the neck and chest. The radial and brachial arteries were sclerotic and tortuous, and the pulse of the two arms was synchronous and of good excursion. The apex beat of the heart was visible in the fifth interspace and was forceful and even. The area of cardiac dullness was normal in size. The sounds of the heart were of fair quality, there was no gallop rhythm and there were no murmurs. The aortic second sound was accentuated. Estimations of the blood pressure in the four extremities were as follows: Right arm 240/140 mm. Hg, left arm 240/140, mm. Hg, right leg 270/160 mm. Hg, left leg 270/160 mm. Hg. The abdominal examination showed nothing significant, the descend-

ing aorta could be felt pulsating. The white cells in the blood numbered 7,000 per cubic millimeter. A probable diagnosis of dissecting aneurysm of the aorta was made. This opinion was further supported by fluoroscopic examination of the heart a few hours later, which showed a diffuse enlargement of the aorta below the arch, with pulsations of it anteriorly and not posteriorly. Also during this first day further evidence of a dissecting aneurysm was found by a demonstration of a difference in the venous pressure in the two arms, measuring 110 mm. water in the right arm, and 350 mm. water in the left arm.



Fig. 4.—Roentgenograms taken in anteroposterior position on the first, thirty-first, and forty-third days of illness.

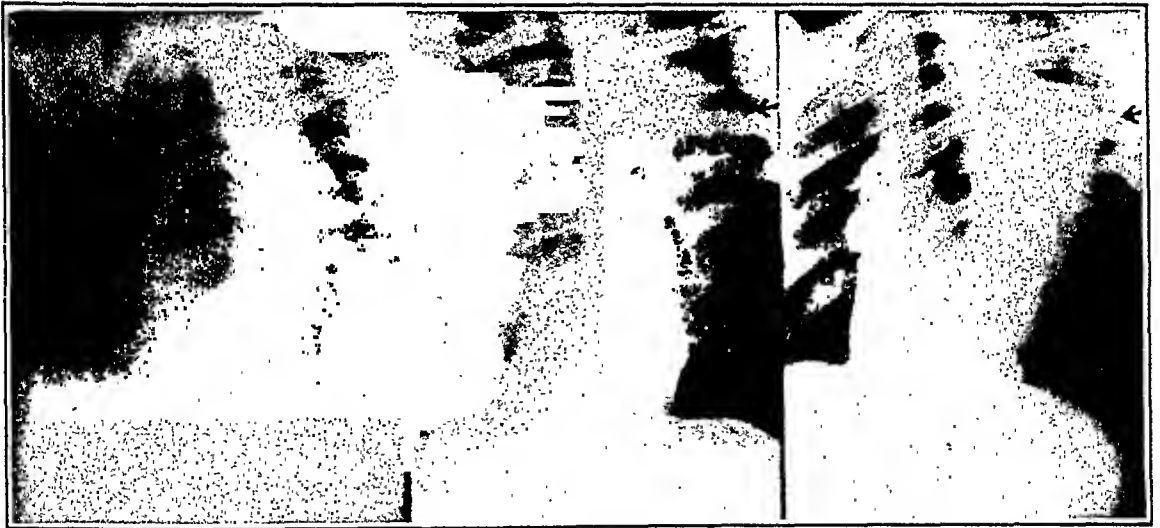


Fig. 5.—Roentgenograms taken in the right oblique position on first, thirty-first, and forty-third days of illness. Note the local bulge where the final rupture occurred.

Course.—The patient remained in the hospital for fifty-three days prior to death and further observations of interest are presented in Figs. 1 to 7. The Wassermann reaction of the blood was negative on three occasions. In the first part of the patient's illness albumin was present in the urine and later it was absent. Serial electrocardiograms (Fig. 1) taken on the first, second, seventh and tenth days showed no evidence of coronary occlusion. In Fig. 2 is a record of the variations in temperature, white blood cell count, and sedimentation rate of the blood. The number of white cells in the blood was usually elevated but was within normal limits on the day before death of the patient. The sedimentation rate of the blood was ab-

normally rapid on four estimations. In Fig. 3 is shown the daily variation in the systolic blood pressure in the two legs. The diastolic blood pressure remained parallel to the systolic. On the seventh day pulsations in the right femoral artery ceased for two days, but returned later; however, the blood pressure in the right leg remained at a lower level than that in the left leg for a period of about six weeks. The cause of this occlusion is shown in Fig. 7 to be a large thrombus surrounding the right iliac artery. In Figs. 4 and 5 are shown roentgen ray examinations of the heart on the first, thirty-first, and forty-third days, in anteroposterior and right oblique views. In the oblique view a



Fig. 6.—Photograph of the heart and upper aorta. The intimal tear has been cut into and appears just above (a); behind it may be seen the deep sac and the opening of the external rupture.

saccular outpouching of the adventitia can be seen in the aneurysm and the pointer shows about where final rupture occurred into the left pleural cavity on the fifty-third day.

During the first week of his illness the patient suffered with pain to the extent that morphine was required frequently to give him comfort. When the occlusion of the right iliac artery occurred (seventh day) he had a mild pain and numbness in the right leg and it became cool to the touch. This lasted only two days and ceased coincident with the gradual return of pulsations in the right femoral artery. Often during his illness the patient would have a moderate exacerbation of the abdominal

pain, but it was never as severe as the original pain. Changes in the physical examination were scarce. In the third week an area of dullness was noted in the upper dorsal chest and the area gradually increased in size during the weeks prior to death. The patient improved subjectively during his hospitalization and on the fifty-second day and fifty-third day he was allowed to sit in a chair. He died suddenly and quietly during the night in bed, fifty-three days after the onset of his disease.

Post-Mortem Examination.—Necropsy showed death to have been caused by rupture of the aneurysm into the left pleural cavity. The pleural space contained about three liters of blood. The final rupture of the aorta occurred in the outpouching

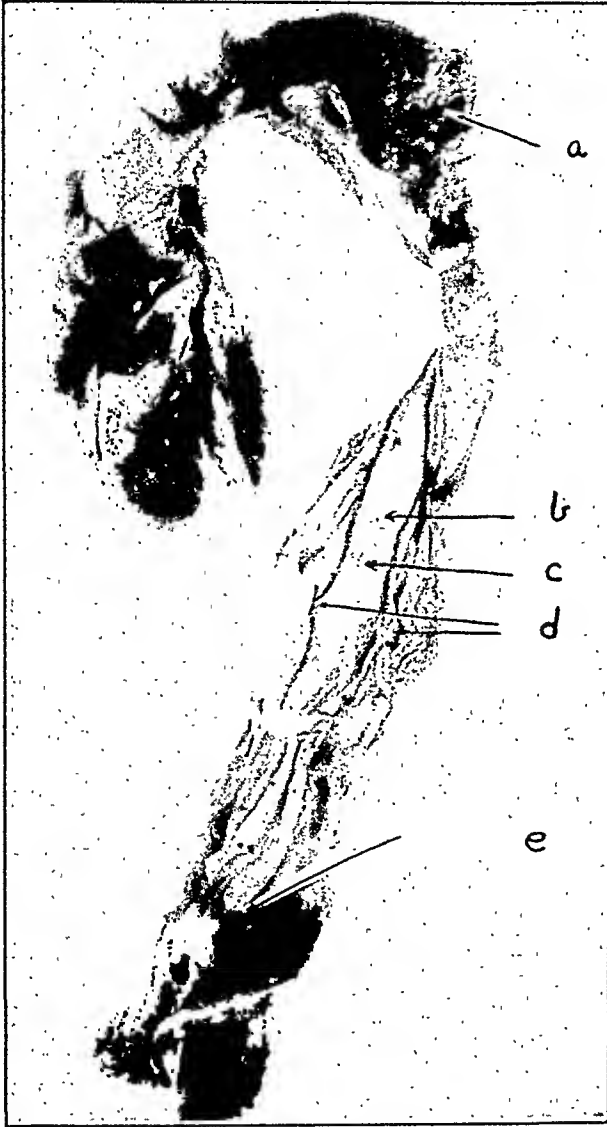


Fig. 7.—Photograph of the heart and entire aorta. (a) Site of rupture into left pleural cavity. (b) Orifice of celiac axis from which the vessel was torn by the dissecting column of blood. (c) Orifice of superior mesenteric artery. (d) Renal arteries; they were not torn loose. (e) Pointer in the orifice of the right iliac artery and below the pointer may be seen a large laminated blood clot.

shown in Fig. 5. This sac contained a laminated thrombus adjacent to the point of rupture, the tear measuring 2 by 0.25 cm. It was located in the anterior wall of the aorta, was diagonally situated and was 16 cm. distal to the aortic valve (Figs. 6 and 7). The dissecting column of blood had torn away several intercostal arteries and also the celiac axis and superior mesenteric artery (Fig. 7). However, no change due to deficient blood supply was visible in the intestines because the lumens of these large vessels were patent into the external column of blood and no thrombi were

present. The dissection of the aortic wall continued downward to and around both iliac arteries and a large laminated clot (6 by 5 cm.) surrounded the right iliac artery (Fig. 7).

The heart was not enlarged, weight was approximately 350 gm. The coronary arteries were patent and only slightly sclerosed. The aorta showed no evidence of syphilis grossly or microscopically and showed moderate atheromatous changes. Microscopic sections of the aorta showed that the dissection took place between the middle and outer thirds of the media, the usual location.

COMMENTS

In the past six months three thorough reviews,^{4, 5, 6} of this subject have been published. Roesler and his coworkers have accepted 17 cases of dissecting aneurysm of the aorta diagnosed ante mortem and proved by autopsy. Seven other cases should be added to this number; another case reported by White and his associates;⁴ three recently reported by Paullin,⁶ one reported by Blackford and Smith,⁷ one diagnosed by Vaughan and reported by Samson,¹ and one reported by Gurin and his coworkers,⁸ diagnosed and proved at operation. These with the case reported bring the total number to 25 reported cases correctly diagnosed ante mortem and proved.

SUMMARY

A case of dissecting aneurysm of the descending aorta is reported in which the diagnosis was correctly made and in which observations on the patient were made during fifty-three days prior to death.

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SPONTANEOUS RUPTURE OF THE AORTA WITH HEMOPERICARDIUM CAUSED BY COARCTATION

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COARCTATION or stenosis of the aorta (adult type) can be described as a congenital maldevelopment of the descending arch of the aorta either at or just below the insertion of the ductus arteriosus. The coarctation may vary in degree, from a moderate narrowing of the great blood vessel to an abrupt constriction and, in some cases, complete obliteration. Clinically, coarctation of the aorta is marked by the development of a collateral circulation the extent of which is dependent on the severity of the stenosis, with forceful pulsation in the episternal notch and carotids, retardation or absence in the femorals and tibials, and hypertension in the upper extremities in conjunction with a decreased blood pressure in the lower part of the body. Abbott¹ believes the presence of these signs alone justify a tentative diagnosis of stenosis. Other investigators have emphasized the value of roentgen examination and electrocardiographic study as confirmatory evidence. The x-ray film may show erosion or scalloping of the under surface of the ribs, depending upon the size and vigorous pulsations of the collateral vessels, hypertrophy of the heart particularly of the left side, dilatation of the ascending aorta, absence of the normal aortic knob and dilatation of the first part of the aortic arch. Fray² feels that it is possible to establish the diagnosis in almost every case where a complete x-ray study of the heart and aorta can be made. There have been a number of cases of coarctation reported in recent literature, the diagnosis based entirely on clinical and x-ray findings.³⁻¹¹

The case to be presented is one of extreme stenosis (adult type) of the arch of the aorta with death caused by spontaneous rupture of the ascending portion and resulting hemopericardium. In analyzing the modes of death from coarctation, Abbott¹ found spontaneous rupture occurring in only 33 cases in a series of 200. There have been four cases reported since 1928.¹²⁻¹⁵ Although the diagnosis of coarctation was not definitely made previous to autopsy, it was suspected as the possible causative factor of the massive pericardial effusion which obscured the heart signs.

CASE REPORT

C. McL., an unmarried white male of nineteen years, was admitted to the Delaware County Hospital on Oct. 13, 1935, complaining of pain in the upper portion of the chest, the lower part of the neck, and a "thumping" above the sternum, these symptoms having developed suddenly during his attendance at an evening outing in a park adjacent to the hospital. There was no history of weakness or disturbance

of circulation in the lower extremities. During high school, the patient was above the average in scholastic ability and his athletic activities included the winning of the school letter in basket ball and football. Following an attack of measles at the age of eight years, a physician apparently told the mother that the patient had "heart disease," but of minor importance. In 1934, during a routine physical examination for freshmen in college, it was discovered that he had high blood pressure which was again noted approximately ten months later when he attempted to obtain a position. His father died of heart disease; the mother was living and fairly well; one brother and one sister were living and well.

On Oct. 15, 1935, the writer was called to see the patient in consultation with Dr. H. Lennox H. Dick. Examination revealed a well-developed and well-nourished young man, sitting upright in bed, who was dyspneic, slightly jaundiced, and who appeared gravely ill. There was marked pulsation with a distinct thrill over the right side of the neck about one inch above the clavicle and a similar finding in the suprasternal notch. The upper limit of cardiac dullness was not determined as it seemed to extend into the neck. In the second interspace, dullness extended 4 cm. to the right of the midsternal line and 5 cm. to the left; in the fourth interspace, 3 cm. to the right; left border 14 cm. to the left where the apex beat was distinctly felt. Point of maximal impulse was located in the fifth interspace about 11 cm. from the midsternal line. The heart sounds were regular and rapid, with a loud, rough, systolic murmur over the body of the heart, the aortic area, and on the left side posteriorly beneath the scapula. The blood pressure at this time was 190/150 in the left arm and 130/90 in the right as compared to 194/129 on admission (arm not stated); blood pressure in the lower extremities was not attempted because of the grave condition of the patient. The pulse rate was 128 and the temperature 98. The lungs were clear. A diagnosis of large pericardial effusion or hemopericardium due to rupture (cause undetermined, possibly coarctation of the aorta) was made.

Laboratory examination showed the blood count to be average, except for a white count of 18,400 with 81 per cent neutrophils; the blood Wassermann and Kahn were negative. Blood chemistry, nonfasting, showed sugar 117.5 mg., urea nitrogen 25.2 mg., and creatinine 1.6 mg. The urine was clear.

An x-ray film of the chest taken Oct. 14, 1935, by Dr. Paul Bishop, showed marked enlargement of the heart, the right side more than the left. The aorta was widened but there was nothing to suggest aneurysm. The lung fields were relatively clear except for some trunk shadow which was probably circulatory in origin. Two days later the chest x-ray was repeated with some increase in the size of the heart noted and a very definite increase in the vertical diameter of the left side of the heart with obliteration of the major portion of the concavity of the left border and heart vessels. This change in so short a time was in support of the diagnosis of pericardial effusion.

Electrocardiographic study of October 16, revealed a P-R interval of 0.10 second; there was a suggestion of a Q-wave in Lead I and a definitely positive Q-wave in Lead III. The T-wave was erect in Leads I and II, inverted in Lead III, and diphasic in Lead IV. There was a marked elevation of the RS-T segment in Leads I and II. The tracing was suggestive of marked myocardial damage and pericardial irritation.

Paracentesis of the pericardium was attempted on October 16 but no fluid was obtained and the patient's condition was not altered by the procedure. His pulse was rapid, the heart action and signs were the same as previously noted. On the following day, October 17, the general condition of the patient was unimproved; the apex beat was still located in the fifth interspace about 14 cm. from the midsternal line; the murmurs were present and there was a thrill on palpation over the sternocleidomastoid muscle. During the day, his blood pressure dropped to 130 systolic in the right arm and 150 systolic in the left. The patient expired suddenly at 9:45 P.M.

AUTOPSY REPORT BY DR. A. D. WALTZ

The body was that of a white male, nineteen years old, about six feet tall, well developed and of an athletic build. No difference could be detected between the development of the upper and lower extremities.

On opening the chest, the pericardial sac was found to extend from the left chest wall to a point about 3 cm. to the right of the sternum, and from the clavicle

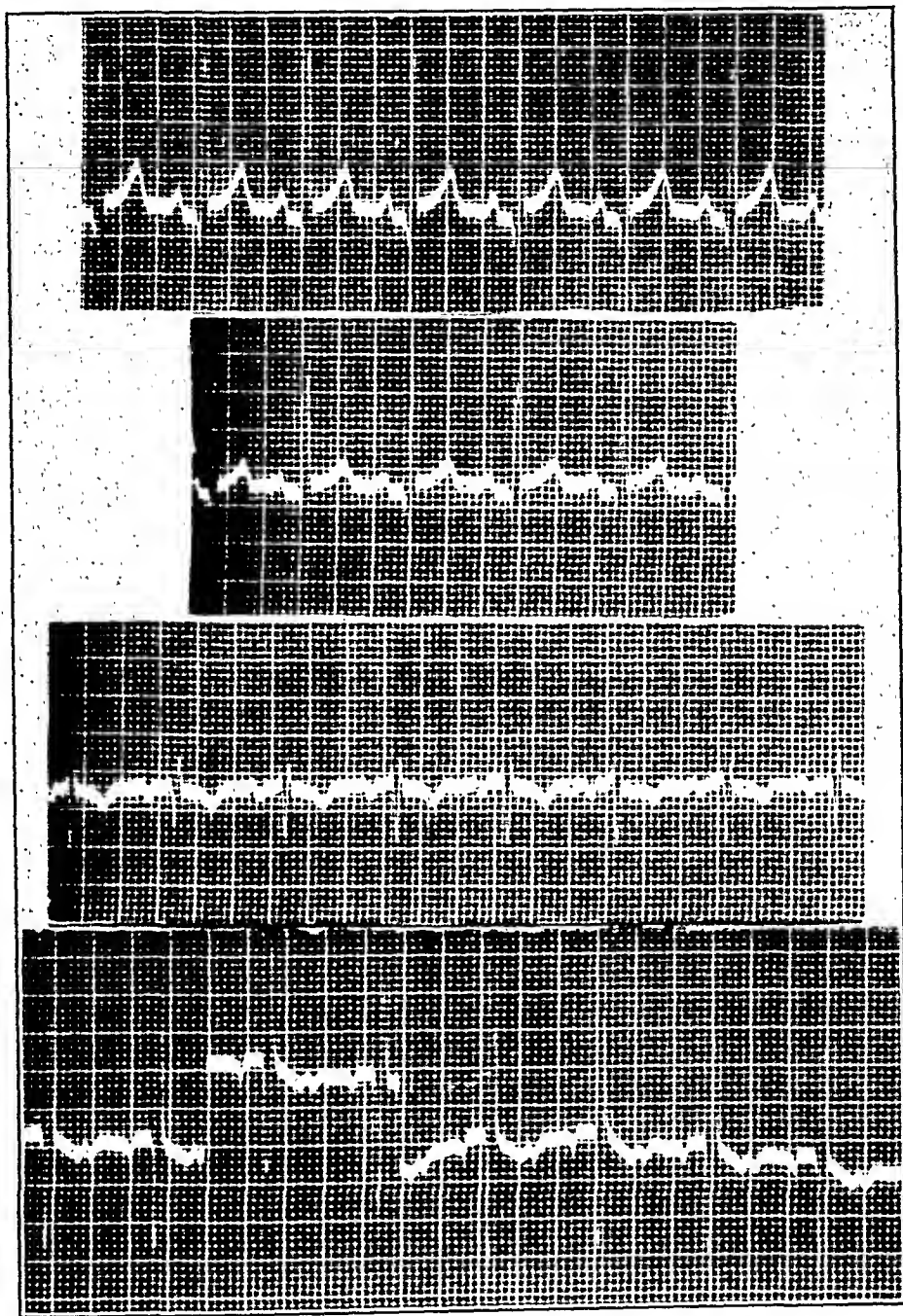


Fig. 1.—Electrocardiogram showing marked elevation of the RS-T segment in Leads I and II, particularly Lead I. Note the practically normal chest lead.

to the fifth intercostal space, measuring 21 x 19 x 10 cm. The pericardium contained a huge blood clot (495 gm.) surrounding the heart. The heart measured 14 x 12 x 9 cm. and with the pericardial sac weighed 770 gm. The total mass, heart and the blood clot within the pericardium, weighed 1,265 gm. The heart was removed with a portion of the descending aorta. The aortic arch was dilated to 4.8 cm. in diameter; the descending aorta was kinked and narrowed at a point 1 cm.

distal to the left subclavian artery. The lumen at this point was nearly occluded by a diaphragm-like obstruction with a central opening only 0.5 cm. in diameter. The aorta below this point was 1.8 cm. in diameter, definitely smaller than normal. The arch of the aorta showed a diagonal, zigzag tear in the posterior wall 2 cm. long, 1 cm. above the aortic valve. Blood had passed through this tear, burrowed between the adventitia and media of the aortic arch, and produced a dissecting aneurysm which had ruptured into the pericardial sac. The pericardium, the epicardium, the pericardial clot, and the edges of the aortic tear were roughened by early fibrous adhesions. The circumference of the valve orifices were: mitral



Fig. 2.—Arrow indicates the stenosis which has been increased in size during photography. A shows the outer wall of the dissecting aneurysm, mesial to which part of the blood clot can be seen.

valve 9.0 cm., aortic valve 7.5 cm., tricuspid valve 11.0 cm., pulmonary valve 8.0 cm. The thickness of the muscle walls measured: left ventricle 2.3 cm., left auricle 0.3 cm., right ventricle 0.9 cm., right auricle 0.2 cm. The valves were normal and the muscle was red and firm.

The coarctation of the aorta was not discovered until the heart had been removed, therefore no satisfactory study could be made of the collateral circulation to the lower extremities. However, there was no apparent enlargement of the intercostal arteries.

Other post-mortem findings were those secondary to heart failure; congestion and edema of the posterior portion of both lungs, congestion of liver, spleen, kidneys,

bladder and gastrointestinal tract. The anterior portion of the left lung was partially compressed by the large pericardial mass.

SUMMARY

A case with autopsy is recorded of congenital stenosis (adult type) or coarctation of the arch of the aorta in a white, unmarried male of nineteen years, with death caused by spontaneous rupture of the ascending portion of the great blood vessel and resulting hemopericardium. This patient had suffered neither cardiac embarrassment nor disability of any kind previous to the sudden fatal attack. Electrocardiographic study revealed pericardial irritation and confirmed the diagnosis of hemopericardium. The autopsy showed (1) a greatly hypertrophied heart which, together with the blood clot within the pericardium weighed 1,265 gm., the clot alone being 495 gm.; (2) dilatation of the aortic arch and a constriction of the descending portion 1 cm. distal to the left subclavian artery, at which point the lumen was nearly occluded by a diaphragm-like obstruction with a central opening only 0.5 gm. in diameter; (3) a diagonal tear 2 cm. in length in the posterior wall of the ascending aorta, 1 cm. above the aortic valve through which blood had passed producing a dissecting aneurysm which had ruptured into the pericardial sac. The valves were normal and there was no evidence of any infective process. Other postmortem findings were those secondary to heart failure.

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Department of Reviews and Abstracts

Selected Abstracts

Møller, K. O.: The Effect of Cocaine and Procaine on the Action of Adrenalin on Skin Vessels: Vascular Action of Cocaine and Procaine in the Perfused Rabbit's Ear. *Arch. Internat. de pharmacodyn. et de therap.* 57: 51, 1937.

Rabbits' ears were perfused according to the method of Katz, in which the change in pressure required to maintain the flow of fluid through the organ constant is used as an index of change in caliber of the small vessels. The author confirms the fact that perfusion with cocaine (1/1 million in Tryode) augments the constrictor action of adrenalin and finds that procaine does not. Cocaine itself constricts the vessels, but its action in sensitizing the vessels to adrenalin cannot be considered synergistic, since if adrenalin is added first, it does not increase the action of cocaine. The constrictor action of racemic corbasil (3:4-dioxy-nor-ephedrine) is also enhanced by cocaine.

STEELE.

Møller, K. O.: Contributions to the Pharmacology of Corbasil (3:4-Dioxy-nor-ephedrine) With an Analysis of the Effect of Cocaine and Procaine on the Vascular Actions of Adrenalin and Corbasil. *Arch. Internat. de pharmacodyn. et de therap.* 57: 67, 1937.

The author points out that corbasil and adrenalin are optical isomers, and that corbasil is also a vasoconstrictor but a considerably weaker one than adrenalin. The methods used for demonstrating the vasomotor effects were (1) in the extremities, recording of systemic arterial pressure and of pressure in the peripheral stump of the femoral artery maintained by collaterals and (2) in the viscera, the recording of systemic arterial pressure and volume of the organ studied. The author reaches the following conclusions:

1. Fundamental differences exist between the action of adrenalin and its isomer corbasil. Corbasil usually dilates the renal vessels, adrenalin contracts them; corbasil increases the volume of the spleen, adrenalin reduces it. In cats under ether or urethane anesthesia, adrenalin produces a fall in arterial pressure, corbasil a rise.
2. The ratio of action of adrenalin to corbasil differs in different animals.
3. Cocaine increases the pressor action of corbasil as well as that of adrenalin, and this increase is believed by the author to be due partly to the action of cocaine upon the peripheral vessels and to its inhibiting action upon the pressure regulating reflexes in the vasosensory zone.

4. Procaine sensitizes the organism to adrenalin and corbasil to a much lower degree than does cocaine, and the sensitization is supposed to depend exclusively upon inhibition of the blood pressure regulating reflexes originating in the vasosensory zone.

STEELE.

Rein, Hermann: The Physiologic Basis for the Mode of Action of the Experimental Substance "Knoll H 75" (1:p-Oxyphenyl 2. Methylamine-propane). *Klin. Wchnschr.* 16: 790, 1937.

The effect of this drug (trade-mark Veritol) was studied in dogs under pernoctone-morphine anesthesia. Arterial pressure, pulmonary blood flow, venous pressure and the local circulation of the viscera or extremities were recorded optically, and often the flow of blood was recorded by Rein's stromuhr.

Respiration, rate of metabolism, and level of blood sugar were unaffected. The important action of the drug was found to occur when arterial pressure was low (operative shock, hemorrhage, etc.). Under these circumstances a sustained rise of pressure was easily obtained by intravenous injection of as little as 0.5 mg. If the arterial pressure was normal, in the intact animal only a very slight rise, if any, was observed. The inference is that the drug does not interfere with the ordinary reflex regulation of arterial pressure. The vagal type of pulse with slowing frequently occurred; but, if the vagi were sectioned or if the animal was atropinized, a rise of arterial pressure well above normal occurred even if it was at normal levels to begin with. The vagal influence was, in this way, shown to be important in preventing the rise of pressure following the use of the drug.

The site of action of the drug is believed to be different from that of adrenalin for two reasons: (1) the latent time of the reaction is 11 or 12 seconds instead of 7 or 8 seconds for adrenalin, and (2) in instances where adrenalin causes a fall veritot occasions a rise. Rein concludes that the drug may be very useful in operative or infectious circulatory collapse because of its marked activity and low toxicity.

STEELE.

Nielsen, H. E.: Influence of Body Position on the Cardiac Minute Output. *Acta med. Scandinav.* 90: 456, 1936.

In the normal individual the cardiac minute output is increased 10 per cent and the stroke volume, 20 per cent, when the patient changes his position from sitting to lying down. In persons with heart disease the differences increase to 20 and 30 per cent, respectively. The respiratory ventilation with a similar change in position decreases 9 per cent.

KATZ.

Büissemaker, J.: The Influence of Restorative Drugs Upon the Orthostatic Circulatory Collapse at Diminished Environmental Pressure. *Ztschr. f. d. ges. exper. Med.* 100: 808, 1937.

Normal men stood up in a pneumatic chamber at a pressure which corresponded to a height of 6,000 m. In from ten to thirty minutes the arterial pressure began to fall slowly at first, then more rapidly. The subjects exhibited faintness, heaviness of the limbs, air hunger, and dizziness. Just before complete collapse occurred, the drug was given intramuscularly. Drugs with central site of action (cardiazol, neospiran, coramine, corned) restored arterial pressure promptly; those with peripheral action were less effective (sympathol, ephedrine). The author explains the greater usefulness of the centrally acting drugs by an increase in reflex excitability which yields an increase in tone throughout the peripheral circulation—arterioles, venules and capillaries—while the peripherally acting drugs affect only the arterioles.

STEELE.

Böhme, W.: The Action of Ventricular Systole in Accelerating Venous Flow. *Klin. Wehnschr.* 15: 1631, 1936.

With the help of the roentgenkymograph and the indirect roentgencinematograph, there was found in man evidence pointing toward systolic acceleration of venous flow, as previously shown in animals. In high grade mitral and tricuspid insufficiency, the contour of the venous pulse is reversed. These studies emphasize the importance of the systolic suction of the ventricle in aiding venous flow.

KATZ.

Radnai, P., and Mosonyi, L.: The Significance of the Reflex Excitability of the Vagus in Angina Pectoris. *Klin. Wehnsehr.* 16: 228, 1937.

Pulse slowing was studied following eyeball pressure, pressure on the carotid sinus, and in the Valsalva experiment. It was found that these tests indicated increased vagus reflex excitability in patients with angina pectoris. Thus those patients with hypertension and anemia who also had angina pectoris had a higher vagus excitability than those without angina.

KATZ.

Scherf, D., and Schönbrunner, E.: The Pulmonocoronary Reflex in Lung Emboli. *Klin. Wehnsehr.* 16: 340, 1937.

This is a report of two cases with small pulmonary emboli in which marked electrocardiographic changes occurred without evidence of heart damage. This was considered to be due to a reflex coronary vasoconstriction from the lungs.

Electrocardiograms were taken on ten anesthetized dogs during production of small experimental pulmonary emboli. In 3 of these a typical Q_1 -T₁ type of electrocardiographic change was found which is ascribed to reflex coronary vasoconstriction.

KATZ.

Ronchese, F.: Infra-Red Photography in the Diagnosis of Vascular Tumors. *Am. J. Surg.* 37: 475, 1937.

Infra-red ray photography is a valuable method of investigation in the diagnosis of vascular cutaneous tumors in the living, when the presence of blood is doubtful.

AUTHOR.

Cacero, Agustin, and Orias, Oscar: The Phonocardiogram Registered in Special Areas of Auscultation. *Rev. argent. de cardiol.* 4: 71, 1937.

By optically recording the heart sounds (Wiggers and Dean) from the apex, mesocardiac and basal (pulmonic) areas simultaneously with the jugular pulse and the electrocardiogram in twenty healthy young medical students, the following conclusions were drawn:

An auricular sound was recorded in 85 per cent of the cases, with about 29 vibrations per second, lasting for about 0.10 sec., appearing in the records with an amplitude of 6 mm., and following about 0.015 sec. after the beginning of wave "a" of the venous pulse and from 0.034 to 0.046 sec. after the top of P-wave of the electrocardiogram. The average figures for the auricular sound were very similar on the different areas.

The first heart sound had a rather complicated appearance, but upon careful analysis and correlation with the mechanical events a systematization was reached. Its picture was essentially the same over all the investigated areas. Very constantly it was possible to individualize four groups of vibrations forming the first sound: the first of all, formed by only one thick vibration and following immediately after the auricular vibration when these were present, began about 0.008 sec. before the top of R, lasted about 0.035 sec., and showed a vibration frequency of 28, 36, and 24 per second over the apex, mesocardiac area, or base, respectively. The second component, formed by one and a half vibrations, began after the top of R and ended always before the initiation of "c," lasted for about 0.036 to 0.045 sec., and showed a vibration frequency of about 39 per sec. The third component, formed by two vibrations, started always rather sharply, keeping very uniform relations with the beginning of the "c" wave of the venous pulse, thus allowing the assumption that they both are due to the same cause (i.e., the opening of the sigmoid valves and initiation of the ejection phase); it lasts for about 0.050 sec. and shows

a frequency of about 39 per sec. The fourth component is formed by an average of two vibrations not so distinctly separated from those of the preceding group; it starts a short interval before the top of the "c" wave, lasts for about 0.060 sec., and shows a frequency of about 32 vibrations per second. The second and third components have the largest amplitude.

All this apparent complexity may be easily and satisfactorily explained if we assume that in the origin of the first sound two acoustic processes take place in each ventricle: one caused by the sudden contraction of the ventricles and the other by the opening of the sigmoid valves. The term "isometric component" is suggested for the first and the term "ejective component," for the second. Each one of them is modified by accessory influences. The isometric component is affected in its earliest portion by tardy auricular vibrations and by the ventricular impact on the chest wall. The ejective component is modified in its latter portion due to the acceleration of blood during the maximal ejection phase. The combined influence of all this accounts for the registration of the four components just analyzed. If sometimes the first sound shows a more homogeneous character, this is due to a more immediate sequence between two or more groups.

The second sound, although very much simpler than the first one, showed also a rather complex picture. This, however, we have been unable to analyze because, in the absence of the central arterial pulse record, we had not enough reference points to correlate the groups of vibration with the mechanical events. It lasted for 0.094, 0.116, and 0.120 sec. over the apex, mesocardiac area, and base, respectively, and showed a frequency of 36 vibrations per second all over the precordial region. It was recorded with maximal amplitude on the mesocardiac area and preceded by a uniform interval of 0.110 sec. the top of the "v" wave on all the explored areas.

The so-called third heart sound was recorded in 65 per cent of the cases, the average figures for its properties being very uniform over all the explored areas. They were for the apex, mesocardiac area, and base, respectively: duration, 0.117, 0.136 and 0.092 sec.; number of vibrations, 3, 7, 4.7, and 3; frequency, 32, 34, and 33 vibrations per second. It was always recorded after the top of "v" wave and a short interval before the end of its descending limb, consequently, during the final moments of the rapid ventricular inflow.

AUTHOR.

de Chatel, A., and Hussey, R.: *Experimental Investigation of the Electrocardiogram With Esophageal Leads.* *Ztschr. f. klin. Med.* 131: 450, 1937.

P-waves in dogs with the chest opened are bigger in esophageal leads than in any other indirect lead. Partial block between the auricles produced by tying the interauricular band alters the form of the P-wave in esophageal leads and leads from the left chest wall much more than those from the right chest wall. The authors believe that esophageal leads are valuable clinically in diagnosing rhythm and conduction disturbances of the auricles.

KATZ.

Holzmann, M.: *Clinical Observations With Electrocardiographic Chest Leads.* *Arch. f. Kreislaufforsch.* 1: 2, 1937.

This extensive article covering 170 pages contains a detailed description of the experiences of the author with chest leads. He is cognizant of the American literature and confirms in general the views now held in this country. He concludes that there is a definite place for this lead in that it gives evidence of abnormalities when none are present in the limb leads and adds further information when the limb leads are abnormal.

KATZ.

Körner, F.: The Cross Striations of Heart Muscle. *Arch. f. Kreislaufforsch.* 1: 358, 1937.

This is a review of the meaning of the intimate anatomy of the heart muscle. This includes observations of the author which show that histologically the cross striations depict the state of contraction or relaxation of the muscle fiber. In a single field the cross striations are clearly narrower and stain red in acid alizarin blue-Mallory, whereas in the relaxed fibers they are thicker and more differentiated and stain blue in the dye. Closer examination shows that this cross striation is in reality portions of fibrils which run the length of the fibers and from one segment to the next.

KATZ.

Master, Arthur M., Jaffe, Harry L., and Dack, Simon: The Heart in Acute Nephritis. *Arch. Int. Med.* 60: 1016, 1937.

Acute glomerulonephritis is sometimes associated with clinical symptoms of failure of the left ventricle, such as dyspnea, cyanosis, and pulmonary edema. These appear early in the course of the disease; in fact, they may be the presenting symptoms and may occur before there is evidence of renal injury. The involvement of the heart is the result of vascular and not renal damage.

The diffuse vascular change also produces hypertension, which is almost always present in the first week or two of the disease.

Changes occur in the electrocardiogram which indicate myocardial damage, that is, definite abnormalities of the T-wave in Leads I, II, and IV, absence of the initial positive deflection in the precordial lead, and prolongation of the auriculoventricular conduction time.

Acute glomerulonephritis is a systemic vascular disease in which the heart may be seriously damaged.

AUTHOR.

Berliner, Kurt, and Master, Arthur M.: Mitral Stenosis: A Correlation of Electrocardiographic and Pathologic Observations. *Arch. Int. Med.* 61: 39, 1938.

Reports of 113 fatal cases of rheumatic disease of the mitral valve with autopsy records were collected, and the electrocardiograms were analyzed. Associated lesions of other valves were found to be the most important single factor affecting the electrocardiograms.

Notching of the P-wave was found to be the principal electrocardiographic sign of mitral stenosis. Marked increase in height and width of the P-wave, however, was always associated with hypertrophy of both auricles and was therefore found to be common only in cases of mitral stenosis associated with disease of the tricuspid valve, and in these cases the notching was generally more marked.

Right ventricular preponderance was noted in less than half the cases of uncomplicated disease of the mitral valve and therefore cannot be regarded as a characteristic sign of mitral stenosis. Right ventricular preponderance, however, was generally found in the "button-hole" type of mitral stenosis, but still more frequently right ventricular preponderance was due to an associated lesion of the tricuspid valve.

Left ventricular preponderance was never found in any case of mitral stenosis unless disease of the aortic valve also was present. When mitral stenosis was associated with aortic insufficiency, electrocardiographic signs of ventricular preponderance depended solely on the extent of the leak in the aortic valve; in all cases of marked aortic insufficiency with high pulse pressure left ventricular preponderance was present, whether the associated mitral stenosis was slight or marked.

The voltage of the chief ventricular deflection (QRS) in cases of mitral stenosis was never above normal unless aortic insufficiency coexisted. In cases of mitral stenosis with atrophy of the left ventricle, the voltage of QRS was normal.

The electrocardiograms of persons with pure mitral insufficiency without stenosis were distinguished from those of persons with mitral stenosis by a normal or nearly normal P-wave. Auricular fibrillation or auricular flutter never occurred in pure mitral insufficiency, and ventricular preponderance was never to the right.

Complete change from right ventricular preponderance to left ventricular preponderance and vice versa occurred only in cases of mitral stenosis associated with lesions of both the tricuspid and the aortic valve.

A correlation of the post-mortem observations and the electrocardiograms revealed that the electrocardiographic signs of ventricular preponderance, when present, indicated the anatomic relationship of the ventricles correctly in 89 per cent of the cases.

AUTHOR.

Bredt, H.: Can Congenital Heart Disease Cause Morphological Changes in the Pulmonary Circuit? *Klin. Wchnschr.* 15: 1358, 1936.

Congenital heart disease by leading to hypertension in the pulmonary circuit can cause a secondary pulmonary sclerosis which does not involve the smallest branches.

KATZ.

Kreuzfuchs, S.: The Course of the Aorta and Its Measurements in Childhood. *Fortschr. a. d. Geb. d. Röntgenstrahlen.* 54: 396, 1936.

The aortic arch in childhood differs from that of the adult. In adults the arch has a horizontal angulated course with a pretracheal-frontal and a paratracheal-sagittal division. This angular deviation is due to the action of the trachea. When the trachea is deviated to the right, the aorta loses its angle and assumes a diagonal course and is arched as usually depicted anatomically. In childhood the trachea is to the right, and only during puberty does it slowly deviate toward the mid-line. In childhood, therefore, the aorta is arched and diagonal in position.

The adult aortic type gives a characteristic x-ray double limb shadow with intensification of the aortic knob. The infantile aortic type gives a single limb shadow, elliptical in shape. In childhood the aorta must be measured in Fechter's position.

In this way the author found values of the aorta as follows:

10 mm. at 5 years
12 mm. at 10 years
14 mm. at 12 years
16 mm. at 14 years
20 mm. at 20 years

Occasionally the infantile aorta persists into adult life.

KATZ.

Ash, Rachel: Influence of Tonsillectomy on Rheumatic Infection. *Am. J. Dis. Child.* 55: 63, 1938.

An analysis is made of the effect of tonsillectomy on the course of rheumatic infection in 522 children treated at the Children's Hospital between 1922 and 1936.

Tonsillectomy did not prevent recurrences of rheumatic manifestations.

Neither the presence or the absence of tonsils at the time of the initial infection nor the removal of tonsils subsequent to the onset had any demonstrable influence on the incidence of cardiac involvement or the death rate, due consideration being paid to the associated variable statistical factors.

A high incidence of rheumatic exacerbations followed immediately on tonsillectomy performed early in the course of the disease.

Tonsillectomy for the rheumatic child seems to be indicated only when there is definite evidence of disease in the tonsils and not as a routine procedure. The operation should be performed only during an inactive phase of the infection. Associated with the absence of other symptoms, the combination of a normal temperature curve and a normal sedimentation rate of the erythrocytes may be taken as indications of an inactive phase.

AUTHOR.

Cochems, K. D., and Kemp, J. E.: Occupation and Syphilitic Aortitis. *Am. J. Syph. Gonorr. & Ven. Dis.* 21: 408, 1937.

Seven hundred forty-nine male individuals, predominantly white, in all stages of syphilitic infection, and about whom all the necessary data were available, were analyzed according to the physical strain consequent to their occupation and the incidence of syphilitic aortitis. This analysis showed:

The incidence of syphilitic aortitis was greater among individuals of intermediate and heavy occupational pursuits (14.4 per cent) than it was among individuals following sedentary occupations (8.7 per cent).

The incidence of uncomplicated syphilitic aortitis was greater among individuals following the lighter occupations (5 per cent) than it was among those whose work was more strenuous (3.7 per cent).

Aneurysm occurred four times as frequently among individuals following occupations demanding a certain amount of physical exertion (6 per cent) than among those whose occupations were sedentary (1.4 per cent).

The incidence of aortic insufficiency was higher among individuals doing heavy labor (2.1 per cent) than among those whose occupations were light (0.7 per cent).

The incidence of aneurysm and aortic insufficiency occurring together was not influenced by the physical stress consequent to occupation.

MONTGOMERY.

Ernstene, A. Carlton: The Cardiovascular Complications of Hyperthyroidism. *Am. J. M. Sc.* 195: 248, 1938.

A study has been made of the cardiovascular complications in 1,000 consecutive cases of hyperthyroidism.

Clinical or electrocardiographic evidence of organic heart disease was present in 173 patients; 32 others had enlargement of the heart by roentgenologic examination but no other signs of organic heart disease.

Auricular fibrillation occurred in 207 patients. In 96 of these, the arrhythmia was present before operation either in its continuous form or in paroxysms of variable duration, while in 111 it developed for the first time as a postoperative complication.

The factors which influenced the incidence of auricular fibrillation most importantly were the presence of organic heart disease, the age of the patient, the duration of the hyperthyroidism, and the type of goiter. The degree of elevation of the basal metabolic rate had no effect.

Normal sinus rhythm was reestablished spontaneously in one-third of the patients with the continuous form of auricular fibrillation. Quinidine sulphate was administered to one-half of the remaining patients in this group, and in 60 per cent of these reversion to sinus rhythm occurred.

Congestive heart failure was present in 44 patients. The two most important factors responsible for this complication were organic heart disease and uncontrolled auricular fibrillation.

The postoperative mortality was considerably greater in patients who had auricular fibrillation either before or after operation than it was in individuals with normal cardiac rhythm.

AUTHOR.

Veal, J. Ross: The Management of Arteriosclerotic Disease of the Lower Extremities. South. M. J. 31: 54, 1938.

The outstanding considerations of such management are:

1. The disease progresses by definite stages.
2. Early recognition and prompt treatment will relieve many patients and restore them to a useful and at least a partially active life.
3. Gangrene can frequently be prevented by cooperation between physician and patient and the consistent use of simple prophylactic measures.
4. When once gangrene has developed, and its development is inevitable in some cases, reduction of the surgical mortality can be achieved in three ways: (a) By careful preoperative preparation, based on the conception of arteriosclerotic gangrene as a systemic condition first and a local condition second. (b) By all the precautions usually taken to avoid trauma, shock, and hemorrhage at operation plus, in our experience, the use of the circular amputation in practically all cases. (c) By proper postoperative therapy.

MONTGOMERY.

Goldblatt, Harry: Studies on Experimental Hypertension. V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia. Ann. Int. Med. 11: 69, 1937.

Persistent hypertension has been produced in dogs and monkeys by constricting the main renal artery with a special silver clamp. In some of the dogs the hypertension has persisted for more than five years. The type of hypertension produced depends upon the degree of constriction of the renal arteries. Constriction of splenic and femoral vessels and of the superior mesenteric artery has produced no effect on the blood pressure. A number of experiments have been performed in an attempt to explain the mechanism of the production of the hypertension. In six dogs, one or both clamps were released or removed some time after hypertension had developed, with prompt restoration of the blood pressure to the original levels. In three dogs removal of the ischemic kidney also was followed by prompt return of the blood pressure to the original levels. Bilateral nephrectomy did not produce hypertension. Bilateral adrenalectomy with or without supportive or substitution therapy prevented the development of the hypertension or interfered with the maintenance of the hypertension which followed the renal ischemia. The results of these and other experiments indicate that this type of experimental hypertension is due mainly to a humoral mechanism and that the adrenal cortical hormone plays an important part in the production or maintenance of the hypertension.

HINES.

Pilcher, Robin: Pulmonary Embolism. A Statistical Study of Its Incidence in Twelve London Hospitals in the Decade 1925-34. Brit. J. Surg. 25: 42, 1937.

There were 731 cases of fatal pulmonary embolism proved by post-mortem examination. This is 0.105 per cent of all surgical deaths; 0.064 per cent of all medical deaths. The true incidence of pulmonary embolism must, of course, be higher than this. In 473 of the 731 cases a search was made for the site of primary thrombosis, and in 362 evidence in peripheral vessels was found.

MONTGOMERY.

Medical Progress. Clin. J. 66: 345, 1937.

Embolism After the Injection of Varicose Veins.

Westerborn in Sweden analyzed the cases of some 20,000 patients who were given injections for varicose veins. There were 11 deaths from pulmonary embolism. In 6 other cases signs of severe embolism were followed by recovery. More radical

surgical procedures on varicose veins have a much higher mortality. Westerborn found that 6,994 operations on varicose veins were followed by 18 deaths from embolism. In America McPheeters found that 6,671 operations on varicose veins were followed by 36 deaths from embolism—a mortality from embolism of 0.54 per cent.

MONTGOMERY.

Homans, John: Venous Thrombosis in the Lower Limbs: Its Relation to Pulmonary Embolism. *Am. J. Surg.* 38: 316, 1937.

The influences, anatomic and related to life in bed, consequent upon many diseases, injuries, and operations, which lead to thrombosis in the lower half of the body, are fairly well recognized today. Many of them are unavoidable, but most of them can be relieved of some of their bad effects by prophylactic treatment.

Thrombosis once established should no longer be treated by the familiar ice bag and immobilization but by real elevation followed early by gradually increasing exercise. Embolism is more likely to be prevented by forestalling the formation of the dangerous propagating thrombus than by apprehensive immobilization. A further study of deep peripheral thrombophlebitis should be made by both the physicians and pathologists. By such means the apparent tendency today to increase in the incidence of thrombophlebitis may be reversed.

AUTHOR.

Barnes, A. R.: Pulmonary Embolism. *J. A. M. A.* 109: 1347, 1937.

Death from pulmonary embolism is a much greater menace in both medical and surgical cases than is generally realized. Although its cause is not known, some of the factors that predispose to its occurrence are known. Mild premonitory attacks frequently precede the fatal seizure, and it is important that they be recognized. The picture of shock, noted as much as or more commonly than marked dyspnea and cyanosis, may constitute the clinical symptoms of pulmonary embolism. The electrocardiogram may furnish invaluable aid in the diagnosis of this condition and especially in its differential diagnosis from acute coronary thrombosis. Whatever the cause of pulmonary embolism, the most promising avenue of attack is the attempt to improve the rate of circulation and particularly the velocity of venous return from the lower extremities. A comprehensive program looking to that end should be applied, if not to all patients, then to those patients whose condition presents circumstances which are known to predispose to the occurrence of pulmonary embolism. Certain results to date encourage one to believe that if such a program were carried out with uncompromising zeal a very high percentage of deaths from pulmonary embolism could be eliminated, at least following surgical procedures, during the puerperium, and following sprains and fractures. In no aspect of surgery is there such a promising field for lowering surgical mortality. The medical profession is challenged to use at least such measures as are available in the effort to combat the tragic situation presented by pulmonary embolism.

AUTHOR.

Johnston, C. H.: Combined Ligation and Injection Treatment of the Varicose Great Saphenous Vein. *J. A. M. A.* 109: 1359, 1937.

Recurrence in cases presenting incompetent saphenofemoral valves when treated by injection alone or by ligation alone is far too common. Ligation at the saphenofemoral junction, dissecting out, and section of all five branches at that level, and injection of the distal end of the saphenous vein, is the treatment of choice. All

cases in which the saphenofemoral valves are incompetent are indicated for the ligation-injection treatment. Until some newer idea or operations supplants the ligation-injection form of treatment, it must be admitted that it gives the greatest promise of permanent success with the least amount of danger, pain, or mutilation in the more extensive varicose veins.

AUTHOR.

Bird, Clarence E.: The Use of Arteriography of Substitutes for Colloidal Thorium Dioxide. *J. A. M. A.* 109: 1626, 1937.

Because of the possibility that the injection of radioactive thorium dioxide solution may cause late toxic symptoms, other materials for arteriography are preferable. Diodrast, neoskiodan, uroselectan and similar preparations made for excretory urography are nontoxic in the doses used and are quickly excreted. They do not damage the intima of the vessels and do not cause pain on intravascular injection (as does sodium iodide). The density of the shadow cast by diodrast and similar iodine-containing solutions when used for arteriography is not quite so striking as that by thorium dioxide, but is entirely satisfactory.

Accompanying photographs of x-rays of arteriovenous aneurysms show the aneurysms clearly and outline many small arteries.

MONTGOMERY.

Koller, S.: The Mortality of Circulatory and Respiratory Diseases. *Arch. f. Kreislaufforsch.* 1: 225, 1937.

The author presents a statistical assay of 1,600,000 deaths of circulatory origin occurring in England and Wales from 1921 to 1933. He is able to show a seasonal variation in death rate with the peak in winter and the low point in summer.

KATZ.

Holzlohner, E.: The Respiratory Pulse in Man and the Blood Flow in the Veins Near the Heart. *Arch. f. Kreislaufforsch.* 1: 305, 1937.

This is a comprehensive review of the subject with a detailed presentation of data to demonstrate that the heart itself causes a systolic acceleration of blood flow in the veins near the heart. The result is that there is an early filling of the auricle and the ventricle independent of diastolic duration. Changes in systolic power of the heart by altering systolic acceleration of blood flow will in this way alter the filling of the heart. An automatic regulation of filling dependent on the power of ventricular systole is thus provided. This systolic venous acceleration is in reality a form of useful work of the heart. Pneumothorax abolishes this systolic venous acceleration. It is probably modified also in incompetence of the A-V valves. These considerations suggest a clinical utility in recording the respiratory pulse. The author describes a string anemometer which he has used for this purpose. This consists of a small wire suspension in an air passage placed in the optical axis of an illuminated microscope system much as is used in the string galvanometer. The air passage is connected to the nasal passage by tubing as in the hot wire arrangement. This meter can be calibrated.

KATZ.

Ludwig, H.: The Heart Kymogram. *Fortschr. f. Röntgenstrahlen.* 54: 469, 1936.

The author points out that in the roentgenokymogram not only local pulsations were obtained but also rotations and displacements of the whole heart. For this reason care must be taken not to read too much into the curves obtained.

KATZ.

Ludwig, H.: Auricular Flutter in the Kymogram. *Röntgenpraxis* 8: 731, 1936.

In this case it was found that flutter waves of the right auricle and left auricle could be distinguished in the roentgenokymogram. These corresponded in frequency with those seen in the electrocardiogram.

KATZ.

Trumble, Hugh G.: Strategic Points in the Lumbar and Sacral Outflows of the Autonomic System: Sympathetic Denervation of the Lower Limbs. *M. J. Australia* 2: 958, 1937.

The technique is a muscle-splitting abdominal operation without opening of the peritoneum.

The whole operation is performed in twenty minutes or less. The patient may be allowed to sit up out of bed on the fourth or fifth day postoperatively. The author has always observed a persistent increase of the temperature of the skin of the leg.

MONTGOMERY.

Barker, M. H.: The Use of Cyanates in the Treatment of Hypertension. *Wisconsin M. J.* 36: 28, 1937.

The cyanates have been administered over a period of seven years to patients who have been under controlled observation for several weeks or months. Symptomatic variations, blood pressure effects and certain blood chemical observations have been correlated with the concentration of the cyanates in the blood. Taking the group as a whole, slightly more than 50 per cent have shown significant decreases in both systolic and diastolic blood pressure, and these drops of pressure were associated with the elevation of the cyanates in the blood to 6-12 milligrams per 100 c.c. Doses of 0.3 gram of potassium sulfocyanate two to fourteen times per week indicate the individual requirement for constant therapeutic blood concentration.

The best symptomatic and pressure-lowering results were obtained in the menopausal and essential types. The malignant forms were rarely benefited. Occasional hypertensive patients with arteriosclerosis showed good improvement, but many suffered only toxic manifestations. A few cases of chronic nephritis showed satisfactory drops in blood pressure, and an occasional diuresis was noted. Toxic manifestations of fatigue, weakness, mental confusion, disorientation, and nausea were encountered. As a rule, only fatigue was noted and chiefly in arteriosclerotic individuals. No dangerous symptoms or findings were met unless the blood cyanates rose over 20 milligrams.

AUTHOR.

Book Reviews

ORTHODIASCOPY—AN ANALYSIS OF OVER SEVENTEEN HUNDRED ORTHODIASCOPIC EXAMINATIONS. By Chester M. Kirtz, M.D., F.A.C.P., Assistant Professor of Medicine, University of Wisconsin; Cardiologist to the State of Wisconsin General Hospital. New York, 1937, The Macmillan Company. Price \$3.50.

This monograph emphasizes the value of a quantitative determination of the size of the abnormal heart in diastole by means of the orthodiagram. The author presents a detailed and analytical consideration of 1,723 cases on whom mensuration of the frontal plane of the heart by this method is compared with the formula for predicting the normal frontal area (Method of Hodges and Eyster) on the basis of age, height, and weight of the individual concerned. To this there is added the greatest transverse diameter of the cardiac silhouette which is compared with normal figures based on similar prediction tables. From these observations the author has concluded that in patients with evidence of cardiac enlargement to physical examination the deviation of the frontal area is almost invariably above the level of 10 per cent, a figure which, expressed in percentage deviation, is abnormal. The cardiothoracic ratio, used so extensively at present as a sign of enlargement of the heart, was found "worthless."

As the author well states, this method is only an additional aid in indicating the probability of the diagnosis in question being correct or incorrect. It is a pleasure to see him revert back to clinical impressions whenever he is in doubt, despite the detailed measurements obtained, especially so in patients with so-called "uncomplicated" mitral stenosis and in mitral insufficiency.

The book is well written and printed in large type. It is a worthy addition to our literature on diseases of the heart and merits the attention of all those who are not as yet acquainted with these methods of mensuration.

A MONOGRAPH ON VEINS. By Kenneth J. Franklin, D.M., M.R.C.P. Tutor and Lecturer in Physiology, Oriel College. University Demonstrator of Pharmacology. Assistant Director of the Nuffield Institute for Medical Research, Oxford. Springfield, Ill., Baltimore, Md., 1937, price \$6.00, Charles C. Thomas.

The timeliness of this volume of some 400 pages will not be questioned by anyone at all familiar with the recent astonishing growth of interest in the study of the peripheral circulation.

Although comparatively little space is given to a consideration of the clinical aspects of disorders of the veins the book is a mine of information concerning the embryological, anatomical, physiological, and pharmacological facts and theories upon which the clinical study of the subject should be based.

The mere listing of the headings of the more important chapters will perhaps serve to give an idea of the character and scope of the monograph—"The Embryology of Veins"; "The Anatomy of the Venous System, Functionally Considered"; "The Valves in Veins"; "The Amount of Circulating Blood: Blood Depôts"; "Comparative Anatomy"; "The Venules"; "Absorption by Veins and Diffusion From Veins"; "Veins and the Nervous System" (three chapters); "The Heart and the Venous Return"; "The Effects of Hydrostatic Pressure"; "The Effects of the Contraction of Voluntary Muscle Upon Venous Return"; "Respiration and the Venous Return in Mammals; the 'Vis a Fronte'"; "Venous Pressure";

"The Movements of the Blood in Veins"; "Clinical." One of the last chapters is devoted to a discussion of the various photographic techniques applicable to research on the venous system.

The book is freely illustrated and has a very extensive bibliography. In the opinion of the reviewer it constitutes a major contribution to the study of the circulation, both central and peripheral.

PATHOLOGIE DES KREISLAUFS. Ein Lehrbuch der Herz und Gefäßkrankheiten von Prof. Dr. Theodor Brugsch, Berlin. Professor der Medizin und Direktor a. D. der Med. Universitätsklinik Halle-Wittenberg. 92 illustrations, 2nd edition, Leipzig, 1937, price, RM 30, S. Hirzel.

The scope of this book of 747 pages is wider than the general reader is likely to associate with its title, the "Pathology of the Circulation." It deals with the disorders of the heart, the peripheral blood vessels, and the general circulation, and few items concerning these have escaped at least a brief consideration, ranging from rare congenital anomalies of the heart to varicose veins of the extremities. More than five-sixths of the text is devoted to matters pertaining to the heart directly, the remainder to the peripheral vessels. The first, or the analytical, portion of the book contains sections on the normal anatomy and physiology of the various components of the cardiovascular system, on cardiovascular symptoms and signs, on the mechanism of the heart sounds, murmurs, pulse, arterial and venous pressures, and on special techniques employed in diagnosis. The space allotted to arterial and venous sphygmograms which are now rarely used in clinical diagnosis might have been more profitably used to amplify the sections on fluoroscopy and electrocardiography, especially the latter, the treatment of which does not seem adequate (9 pages with very few illustrative records). The first 160 pages of material are presented as the groundwork for the comprehension of the numerous clinical varieties of cardiovascular disorders to which the remainder of the book is devoted, namely, various forms of vascular collapse, cardiac insufficiency, the arrhythmias, valvular disease, coronary disease, and such other sections as are found in standard textbooks on heart and vascular diseases. The section on "Constitution and Circulation" is well worth reading.

The manner of treatment of some of the material reveals conflicting influences. On the one hand, the author stresses the need of evaluating the status of a cardiac patient, not only by a structural, a physiological, or a functional derangement, but by all of them considered together in the light of the constitutional type to which the individual belongs. Some of the sections, however, disclose a strong influence by an opposite point of view when extensive discussion is given not only of the diagnosis but of the prognosis and treatment of valvular lesions. Consideration of cardiac diseases in this fashion serves to obscure the fact that the valve damage is only an element in a disease and not the disease itself. The study of the natural history of heart diseases in recent years, especially that of rheumatic fever, in which the object of attention is not so much the evolution of an endocardial or myocardial injury, but the life and activity of the subject, has thrown considerable light on prognosis and treatment. One misses such discussions of natural history in this book. Except for an occasional reference, there is no bibliography.

The quality of the material is uneven. The sections on treatment are perhaps, on the whole, the weakest. The 38 pages devoted to digitalis presents an unusual number of generally abandoned theories, statements without adequate support, and specific therapeutic recommendations without sound basis in theory or practice. A few of these may be mentioned by way of illustration. Chronic cardiac insufficiency, the author maintains, is abolished by 1½ gr. of digitalis daily for ten days. In his method of using large doses for the treatment of severe heart failure he recommends 6 gr. daily for two days, 4½ gr. for two days, and 3 gr. for three days, and

warns against such large (?) doses if the patient has received digitalis during the previous week. In the use of this method, he maintains, the infusion of digitalis is the most suitable preparation in the first two to three days. He states that if, during the course of left heart failure, the right heart also fails, causing general venous stasis, intravenous strophanthin is preferable to digitalis. He states that digitalis dilates the renal vessels and perhaps also stimulates the renal parenchyma, and that the proprietary preparation, digipurat, has a greater action on the kidney. He strongly recommends intravenous strophanthin therapy and states that in decompensation due to valvular diseases the dose depends upon the valve involved: 0.5 mg. strophanthin in mitral insufficiency, 0.4 mg. in aortic insufficiency, 0.2 to 0.3 mg. in mitral stenosis. He states that a brief course of digitalis will restore compensation which has failed as the result of valvular disease, whereas in "pure" cardiac insufficiency the continued use of digitalis is necessary. To counteract the excessive slowing by digitalis he recommends atropine and thyroid, and to counteract coronary constriction he recommends a mixture of caffeine, theobromine, and papaverine. Such thoughts, presented, as they are, without evidence, will for the most part seem strange and unattractive to the critical student of cardiovascular disease.

The style of the book is fairly direct and usually interesting. Many of the discussions are thought-provoking. The author's inclination to rather liberal speculation, however, makes this book safer in the hands of the critical and experienced cardiologist than in those of the average student or practitioner for whom the author states the book is intended.

MACLEOD'S PHYSIOLOGY IN MODERN MEDICINE, ed. 8, edited by Philip Bard. St. Louis, 1938, The C. V. Mosby Company.

The section on the circulation, covering 226 pages, was written by H. C. Bazett. The amount of material presented is extremely large, and the descriptions are very detailed. This textbook of physiology contains information concerning the circulation which is larger in amount, more detailed, and more up-to-date than that which is to be found in any other book with which this reviewer is acquainted. A large bibliography is provided. The sections on cardiac output, on blood velocity, on pulse wave velocity, and on the reactions of cutaneous vessels are very well done, and the value of the newer data is assessed from a point of view possible only to an active investigator. A section on hemorrhage, oligemia, plethora, shock, and cardiac abnormalities is written from a viewpoint which shows that the author has not lost his interest in clinical medicine.

The presentation differs from that in most textbooks in that it places more emphasis on the physical point of view. This will make certain sections hard reading for those who are unfamiliar with physical and mathematical conceptions, as most practicing physicians are. The diction might be clearer. Its great value will be as a book of reference for clinicians who have no time to read the ever increasing bulk of original physiologic literature.

ISAAC STARR.

LEHRBUCH DER ELEKTROKARDIOGRAPHIE. von Dr. D. Scherf. Privatdozent für Innere Medizin an der Universität Wien. 169 text illustrations, Vienna, 1937, price RM 16.50, Julius Springer.

Dr. Scherf has written a very serviceable book in "Lehrbuch Der Elektrokardiographie." The plan of the book follows the conventional method. It begins with the general principles of electrocardiography, the apparatus and description of the normal electrocardiogram and its variations. Then follows a section describing abnormalities of the form of the electrocardiogram, correlating diseases with the electrocardiographic changes in a very satisfactory fashion. He follows the middle

ground of presenting the conventional or "old terminology" of bundle-branch block, but also gives the "new terminology." In the section having to do with coronary occlusion and coronary artery disease, precordial chest leads are discussed. The section which is given over to the irregularities is very well done, except for those parts having to do with treatment. These appear to me to be inadequate and not especially judicious, probably because the plans of therapy do not coincide with my own notions of the use of the measures and drugs which are available. The use of illustrations has been very generous. The bibliography has not been selected with as much care as the rest of the book deserves.

The volume is a very welcome addition to the library of those especially interested in electrocardiography, but it will find little place outside this group in this country since our own literature abounds in excellent texts for students and practitioners.

The appearance of a second, revised edition of the book within a few months of the printing of the first edition testifies to the popularity that it has won.

A DISSERTATION ON ACUTE PERICARDITIS. By Oliver Wendell Holmes, M.D. January 12, 1836, 39 pp., 12 mo., Boston, The Welch Bibliophilic Society, 8 Fenway, price \$7.50. Introduction by James F. Ballard, Director, Boston Medical Library.

Oliver Wendell Holmes, after having graduated from Harvard College in 1829 and having read law for a year, decided to take up the profession of medicine. After taking two courses in a private medical school in Boston he went to Paris where for two years he walked the wards of La Pitié and the Hôtel Dieu in the footsteps of two great clinicians Louis and Andral. Returning to Boston late in 1835, he was given the degree of M.D. by Harvard in 1836 and as one of the requirements for that degree offered this dissertation on pericarditis.

By some strange circumstance the manuscript of this essay has remained all this time unknown and unpublished in the archives of the Boston Medical Library and has only now seen the light of day in this publication by the Welch Bibliophilic Society.

The writer presents an analysis of the anatomical and clinical features of eleven cases observed with Andral and Louis, as well as of a larger number of cases recorded by Bouillaud, and discusses the value of the "antiphlogistic" treatment in general use at that time.

He quotes Bouillaud as stating that "of twenty patients attacked with acute general rheumatism of the articulations, there will be at least half who will offer the symptoms of pericarditis or endo-carditis (inflam. of the internal membrane of the heart) and often of both united."

The volume is an attractive, finely printed brochure of forty pages which should be warmly welcomed by medical bibliophiles as well as by all who are interested in the history of this important disease.

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THE CAUSES OF DEATH IN PATIENTS WITH CONGESTIVE HEART FAILURE*

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MORTALITY statistics indicate that heart disease is the cause of death about twice as often as is any other condition. Cabot¹ analyzed 4,000 clinical and post-mortem records of patients dying at the Massachusetts General Hospital between 1896 and 1919 and found cardiovascular disease an important factor in 1,520 (38 per cent) of these individuals. This and other studies indicate that during the last few decades the number of deaths resulting from cardiovascular disorders has materially increased. For example, White² states that in Massachusetts the death rate from heart disease per 100,000 was 124 in 1915, 215 in 1925, and 341 in 1935. Such figures excite the query as to the cause of this striking increase. During the same period that the increase in morbidity and mortality has occurred, much time has been devoted to the study of heart disease and many valuable contributions have been made relative to the diagnosis and treatment of this condition. The factors usually mentioned to account for the apparent paradox are (1) the more frequent recognition of cardiac deaths in recent years; (2) increased life expectancy, which favors the more frequent development of degenerative heart disease; and (3) an increase in the "stress and strain" of life.

Assuming that a significant increase in morbidity and mortality from heart disease has occurred, the following questions are pertinent: (1) When heart disease is present in an individual, what factors, circulatory or noncirculatory, actually produce death? (2) What is the effect on these factors of the modern methods of treating congestive heart failure? (3) Is life prolonged by the use of these treatment methods? With these questions in mind the present study was undertaken.

METHOD OF STUDY

An analysis was made of the clinical and pathologic records of patients who gave a convincing history of congestive heart failure and

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TABLE I

CAUSES OF DEATH IN PATIENTS WITH CONGESTIVE HEART FAILURE

TYPE OF HEART DISEASE	GROUP	NUMBER OF CASES	INCIDENCE %	AVERAGE AGE AT DEATH (YEARS)	AVERAGE DURATION OF ILLNESS (YEARS)	EDEMA AT DEATH [‡] %	MYOCARDIAL EDEMA %	CHIEF CAUSES OF DEATH										SUPPLEMENTARY CAUSES OF DEATH	
								1 st UNCOMPLICATED CON- GESTIVE HEART FAIL- -URE	2 nd (DAYS IN HOSPITAL)	PULMONARY EMBOLISM AND INFARCTION	PNEUMONIA	UREMIA	CEREBRAL VASCULAR ACCIDENTS	SEPTICEMIA	CORONARY DISEASE	MISCELLANEOUS	PNEUMONIA [‡]	PULMONARY EMBOLISM AND INFARCTION	
Hypertensive heart disease	A	36	25	44	8	75	69	9	15	10	15	30	10	0	0	5	45	40	
Arteriosclerotic heart disease	A	14	17	38	18	36	50	14	14	20	14	0	0	7	14	0	50	50	
Arteriosclerotic heart disease with hyper- tension	B	14	13	65	40	26	16	7	0	12	44	21	0	0	0	0	64	51	
Syphilitic aortic insuf- ficiency	A	12	15	44	12	33	25	0	0	41	0	0	0	0	0	0	8	41	
Rheumatic heart dis- ease	B	12	12	43	11	50	22	25	16	25	25	0	0	0	0	11	47	52	
Miscellaneous	A	12	15	44	12	33	25	0	0	41	0	0	0	0	0	0	55	67	
	B	12	12	43	11	50	22	25	16	25	25	0	0	0	0	11	47	52	
Total	A	81	100	51	11	53	48	9	23	32	11	21	2	9	0	0	35	44	
	B	104	100	47	18	30	34	9	9	14	16	21	8	5	0	0	53	23	

*Patients dying during 1926-1930.

†Patients dying during 1931-1935.

‡Median duration of life in months, after the onset of congestive symptoms.

§Patients with moderate or marked edema.

||With or without endocarditis.

‡Total per cent, both as a primary and secondary cause of death.

who died and were subjected to post-mortem examination at the Vanderbilt University Hospital during 1926-1935. Only records of patients who had exhibited definite evidence of congestive failure at some time during the course of their disease and showed cardiac dilatation on post-mortem examination were included in this study. By limiting our material in this manner, we felt that in the group studied most of the factors which produced death would be related either directly or indirectly to cardiac disease.

In order to compare recent treatment results with those previously obtained in this clinic, the records of the patients dying of heart disease during 1931-1935 (Group B) were compared with those of 1926-1930 (Group A), (Table I and Fig. 1). The types of heart disease were classified as follows: hypertensive, arteriosclerotic (with or without hypertension), syphilitic aortic insufficiency, rheumatic, and miscellaneous. The latter group included a variety of conditions such as cor pulmonale, thyrotoxic heart disease, concretion cordis, congenital heart disease, gumma of the myocardium, myocardial infarcts following coronary embolism, etc. In some patients more than one form of cardiac disease existed, but usually one predominated, and this determined the classification.

In each case were noted the age of the patient at death, the duration of life after the first appearance of congestive failure, the amount of subcutaneous edema at death, and whether either the lungs or the liver showed congestion. Because of our interest in the mechanism of the beneficial action of diuretic drugs, the presence or absence of myocardial edema, as revealed by microscopic examination, was noted. An attempt was made in each case to determine the chief cause of death. This was found to be difficult in some instances. However, after considering the opinion expressed by the pathologist at the time of post-mortem examination concerning this point and after reviewing the clinical and pathologic records, we believe that this has been done with reasonable accuracy. It is true that in some subjects there were a number of conditions present, no one of which, had it operated singly, would probably have been sufficient to cause death. One usually was preeminent, however, and in our study this condition was designated the cause of death. Because of the frequency of pulmonary embolism and infarction and of pneumonia as supplementary causes of death, the total incidence of these was also recorded (Table I).

RESULTS

Incidence.—There were eighty-one cases during the years 1926-1930 and 104 during 1931-1935, which fulfilled the requirements mentioned above. In the latter series there was a relatively greater incidence of cases in the hypertensive and the rheumatic groups and a slight decrease in the other groups. The distribution of the various types of heart disease was found to correspond closely to figures given in other reports

from the South,^{3, 4, 5} the vascular diseases constituting about 60 per cent and the rheumatic and syphilitic diseases, each about 15 per cent.

Age at Death.—The average age at death was between 35 and 45 years for all types of heart disease except the arteriosclerotic, in which it was about 65 years. It may be observed in Table I that these figures in general are lower for Group B than for Group A. This is due to earlier development of disease in many patients of the former group.

Duration of Life After Onset of Congestive Symptoms.—The median duration of life after the onset of congestive symptoms was found to be eleven months for Group A and eighteen months for Group B (Fig. 1). This increase in duration was present in the hypertensive, the arteriosclerotic and the rheumatic groups. On reviewing the ten-year "after histories" of 1,000 men suffering from heart disease, Grant⁶ found that

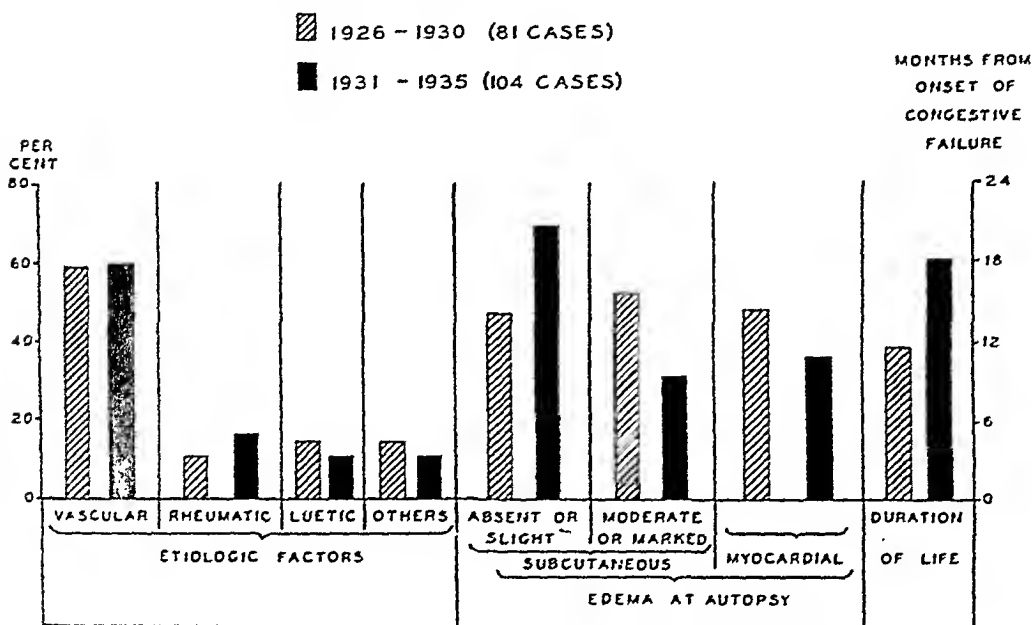


Fig. 1.—Congestive heart failure in cases coming to autopsy.

the duration of life, in the presence of venous congestion was two and one-half years. A large proportion of his patients had rheumatic heart disease. In Group B of our series the average duration in rheumatic subjects was thirty-two months, in the arteriosclerotic subjects forty months, and in the corresponding syphilitic group only eleven months. In manifest syphilitic aortitis Cabot found that, when "once the disease becomes known, it kills in most cases within two years from the first symptoms." On the basis of his study of hypertensive heart disease he concluded that "death usually follows within a year from the first serious evidence of stasis."

Congestion at Death.—Evidence of congestion of the liver and lungs was present in 75 per cent of the patients in Group A and 65 per cent in Group B. This decrease in congestion in Group B as compared with Group A was not as great as the decrease in the amount of edema pres-

ent at death in the members of Group B as compared with Group A. In the 1931-1935 group there was a definite reduction in the amount of subcutaneous edema at death in each type of heart disease, except in the miscellaneous cases, for 53 per cent in Group A exhibited moderate or marked edema as compared with 30 per cent in Group B. A corresponding difference was noted between Groups A and B in the incidence of myocardial edema (Fig. 1).

CAUSES OF DEATH

(Table I and Fig. 2)

The cause of death in most cases was due to congestive heart failure, pulmonary embolism or infarction (or both), pneumonia, uremia, cere-

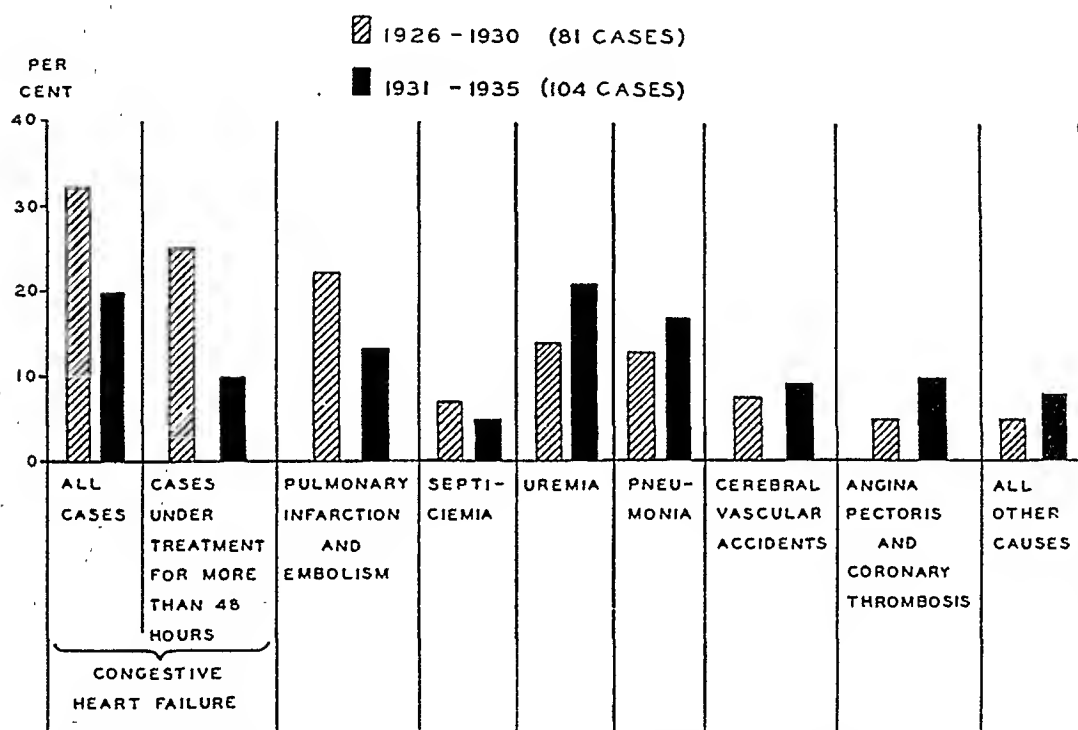


Fig. 2.—Chief causes of death in patients with congestive heart failure (autopsied).

bral vascular accidents, septicemia (with or without endocarditis), angina pectoris or coronary occlusion, and a few miscellaneous conditions. The rôle of each of these factors will be considered separately as follows:

1. *Congestive Heart Failure*.—According to reports in the literature, when once congestive failure has become manifest in patients with heart disease, death will result from congestive failure in from 30 to 40 per cent of the cases. Grant⁶ found that 37 per cent of his patients with syphilitic aortic insufficiency died of congestive heart failure. Cabot¹ found that 34 per cent of his syphilitic patients and 33 per cent of his hypertensive patients died of this cause. Of 107 "pure mitral cases" he states "these cases seem to show that as a rule death does not occur in mitral disease by means of decompensation and passive congestion." Nevertheless, in 106 cases of mitral stenosis he found that forty-nine died of passive congestion.

We were interested in determining the frequency of congestive failure as a cause of death in patients with heart disease since the adoption of our present form of treatment. The incidence of this condition in the cardiac patients who died during 1931-1935 was compared with that of the 1926-1930 group. Whereas congestive failure accounted for 31 per cent of the deaths in the earlier group, it accounted for only 18 per cent in the 1931-1935 patients. We then divided the two groups according to whether the patients had been in the hospital for two days or less when death occurred, since time for response to treatment was usually insufficient if the patient had been hospitalized less than two days. Nine per cent of the patients in Group A, and the same percentage in Group B died of congestive heart failure within two days of admission to the hospital. Among those living longer than two days after their hospital admission, however, congestive failure accounted for 23 per cent of the deaths in Group A and for only 9 per cent in Group B. This pronounced decrease in the frequency of congestive heart failure as the cause of death in the 1931-35 group was observed in each etiological type of heart disease included in our study except the miscellaneous group. Here no decrease occurred. It is noteworthy that in syphilitic aortic insufficiency congestive failure accounted for 50 per cent of the deaths in 1926-1930, whereas it accounted for only 17 per cent in 1931-1935. In the arteriosclerotic type it accounted for 14 per cent in the first period and for none in the latter.

2. *Pulmonary Embolism and Infarction.*—A comparison of the occurrence of pulmonary embolism and infarction as the chief causes of death in the periods 1926-1930 and 1931-1935 reveals a marked reduction for the latter period. This decline is well-defined in the arteriosclerotic types (with and without hypertension) and in the rheumatic and syphilitic types, although there is a slight increase in the hypertensive group.

The incidence of these conditions as supplementary causes of death experienced a marked decrease in each type of heart disease in Group B, having occurred in 44 per cent of the cases during 1926-1930 and in only 23 per cent of the group during 1931-1935.

3. *Pneumonia.*—A definite increase in the incidence of pneumonia in heart disease was noted in Group B. This condition supervened in 35 per cent of Group A and 53 per cent of Group B patients. Sixty-four per cent of the patients with arteriosclerotic heart disease in the group during 1931-1935 developed pneumonia, and it was present in 67 per cent of the patients with syphilitic heart disease. As the chief cause of death pneumonia also showed a definite increase in the rheumatic, syphilitic, and arteriosclerotic groups.

4. *Uremia.*—As a cause of death in the patients with hypertensive heart disease uremia far surpassed all others, accounting for 50 per cent

of the deaths from 1931-1935. In the subjects without hypertension it caused only one death during this period.

5. *Cerebral Vascular Accidents*.—This was the lethal factor in 10 per cent of subjects with hypertensive heart disease in Group A and in 8 per cent in Group B. Cerebral hemorrhage was the condition usually encountered at necropsy. Cerebral accidents appeared with greater frequency in the rheumatic subjects than in the hypertensive ones, being the cause of death in 22 per cent of the former from 1931 to 1935. In these patients cerebral embolism was usually found at post-mortem examination. In a review of 330 cases in which death occurred as the direct result of cardiac disease, Willis⁷ found embolic phenomena in 58 (17 per cent).

6. *Bacterial Endocarditis and Septicemia*.—These were the lethal factors in 6 per cent of patients of Group A and in 5 per cent of Group B. In the latter group 17 per cent of the deaths of patients with rheumatic heart disease were caused by these complications. Here they usually were manifestations of subacute bacterial endocarditis.

7. *Angina Pectoris and Coronary Occlusion*.—Each of the arteriosclerotic groups experienced a high incidence of angina pectoris and coronary occlusion. It is of interest that, whereas coronary disease caused no deaths from 1926 to 1930 in patients with syphilitic aortic insufficiency, it accounted for 17 per cent of deaths in this group from 1931 to 1935. Grant⁶ found that it accounted for 9 per cent of the deaths in eighty-two patients who succumbed to this type of cardiac disease.

8. *Miscellaneous*.—Under this division have been placed a variety of conditions. One patient in the syphilitic group died of a ruptured aneurysm, and two died suddenly, possibly of ventricular fibrillation. Some of the other miscellaneous causes of death were mesenteric thrombosis, heart block, lung abscess, etc.

DISCUSSION

Although the number of cases is not large, the foregoing comparisons of the patients in Group B with those in Group A (Table I) seem to indicate that in recent years there has been a definite increase in the duration of life in patients who have suffered from congestive heart failure. This prolongation of life seems best accounted for by the more effective control of congestive failure. That this was obtained is indicated by the marked reduction in the number of patients during the period 1931-1935 who died primarily of congestive heart failure. This is further indicated by the distinct reduction in the 1931-1935 group of the amount of subcutaneous edema, myocardial edema, and hepatic and pulmonary congestion found at post-mortem examination. It also seems reasonable to attribute the noteworthy reduction in the incidence of pulmonary embolism and infarction in large measure to the better control

of passive congestion. The incidence of pneumonia, on the contrary, has shown a distinct increase. Pneumonia was present in 53 per cent of the subjects in Group B and was the second commonest cause of death in our series. We regard this as being due to the fact that with the better control of circulatory factors in cardiac disease life is prolonged, and, since patients with advanced heart disease are in poor general physical condition, the chances for the development of pneumonia are increased.

The reduction in the incidence of congestive heart failure as a cause of death is reflected not only in necropsy reports, but also by the increased number of patients discharged from the hospital as "improved." Since only about 20 per cent of the patients who entered the hospital with congestive heart failure died in the hospital and since only about 20 per cent of these patients who died were found at post-mortem examination to have congestive heart failure as the chief, immediate cause of death, it is evident that our mortality from congestive heart failure during 1931-1935 was approximately 4 per cent. Of those who were treated in the hospital for more than two days, this mortality was approximately 2 per cent.

If more effective control of passive congestion constitutes the explanation of the better therapeutic results obtained in the 1931-1935 group as compared with the 1926-1930 group, how was it brought about? The management of patients with heart disease as regards activity, diet, fluids, digitalis, and sedatives has remained essentially the same throughout the ten-year period. The only significant therapeutic change made during this period was the more intensive use of diuretics. This began in 1930. Since 1930 every effort has been made to keep patients "dry." All edematous subjects have been tested for tolerance to the various xanthine diuretic drugs, and edema has been treated by the use of the latter for two or three days each week, with or without salyrgan. The latter was employed freely in all cases except those exhibiting evidence of impaired renal function.

A survey of the group of patients who received frequent injections of salyrgan (Group B) reveals that only one, excluding patients with hypertension, died of uremia. Fifty per cent of the subjects in Group B who had hypertensive heart disease died of uremia. Most of these patients had either malignant or benign nephrosclerosis. It seems probable that the better control of edema in these patients protected a certain number from early cardiac death and allowed for progression of the degenerative changes in the kidney to take place. It is also possible that in subjects with occult renal injury the mercurial diuretics may have caused further damage to the kidneys. Wiseman,⁸ however, records the administration of 270 injections of salyrgan to one patient in five years without apparent harm.

The data in Table I (Group B) reveal the cause of death in patients who had manifested congestive heart failure and had received the conventional treatment together with the intensive use of diuretics. In the subjects with hypertensive heart disease uremia stands first as a cause of death; in arteriosclerotic heart disease pneumonia is the outstanding lethal development, although angina pectoris and coronary thrombosis are common; in rheumatic fever embolism and pneumonia are the common terminating conditions, although congestive failure and bacterial endocarditis frequently occur.

The frequent occurrence of pulmonary infarction and pneumonia as supplementary causes of death in each type of heart disease should be emphasized. Impressed by the importance of these complications we have recently reduced the initial period of complete bed rest for our patients with congestive failure and have given careful attention to the problem of the prevention and treatment of respiratory infections.

SUMMARY AND CONCLUSIONS

A study has been made of the cause of death of patients who suffered from congestive heart failure and who had been subjected to post-mortem examination at the Vanderbilt University Hospital. Two groups, composed of patients who died during the years 1926-1930 and 1931-1935, were compared as regards underlying and immediate lethal factors.

Death from congestive heart failure and from pulmonary embolism and infarction distinctly decreased in frequency during the period 1931-1935. During this same period pneumonia, both as a primary and supplementary cause of death, increased in frequency, particularly in patients with arteriosclerotic heart disease.

Comparison of the two groups indicates that the duration of life after the onset of congestive symptoms has been distinctly prolonged in recent years. This is attributed to the better control of edema and has been brought about largely by the intensive use of mercurial and xanthine diuretics.

Intensive treatment with salyrgan did not increase the incidence of uremia in our group of nonhypertensive patients.

Uremia occurred with increased frequency in the 1931-1935 hypertensive group as compared with the 1926-1930 group. Whether the increased incidence of uremia in the subjects with hypertensive heart disease was due entirely to the prolongation of life which resulted from improvement in the treatment of heart disease (intensive use of diuretics), thus allowing progression of renal damage to occur, or whether in some instances the mercurial diuretics actually favored progression of renal disease cannot be stated with certainty.

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SOME PROBLEMS IN THE DIAGNOSIS, PROGNOSIS AND TREATMENT OF ACUTE ARTERIAL OCCLUSION*†

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THE diagnosis of acute occlusion of the large arteries of the upper and lower extremities is seldom difficult. The symptoms and signs attending the abrupt closure of the main artery of a limb are usually of such character that the diagnosis may readily be made by one familiar with the condition. The differentiation of embolism and thrombosis as the cause of the sudden circulatory arrest is a more difficult problem since interruption of the blood flow, common to both embolism and thrombosis, plays such a dominant role in causation of the signs and symptoms present in the condition. It is our opinion, however, that a careful study of the signs and symptoms, particularly the sequence of their development, their location, and their severity, makes possible the differential diagnosis of embolism and thrombosis in the majority of cases. This report is mainly concerned with the symptom of pain in thrombosis and embolism, its possible causes, and its clinical significance. In addition, the prognosis and treatment of acute arterial occlusion are considered in the light of newer methods of therapy.

In a series of thirty-six cases of acute embolic occlusion pain was the initial symptom in twenty-three, or approximately 64 per cent. Pain of maximal severity at the onset was present in nineteen of these twenty-three cases, or approximately 53 per cent of the total. Although pain was the first complaint in the other four cases, it was described as a distress in the limb at the onset, and a definite interval of time elapsed before the pain reached its maximum severity. In six of the other seventeen cases the development of pain, numbness, and coldness appeared to coincide, and in the remaining eleven cases the sequence in the development of symptoms was numbness, or numbness and coldness, followed by pain. To sum up, then: pain was present as the initial complaint in 64 per cent of cases of acute embolic occlusion; it was of maximum severity at the onset in 53 per cent and was present in the later stages of the condition in 100 per cent of cases. It was noted that pain of maximal severity at the onset usually was located at the level of the occlusion, and much less often in the distal part of the affected limb, and that the pain present in the later stages of the condition was always

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located distal to the site of the occlusion. In view of the variation in the time of development, in the location, and in the severity of the pain present in different cases of acute embolic occlusion, it seemed to us unlikely that the origin of the pain could be identical in all instances.

It seems clear from the work of Lewis¹ that pain developing distal to the site of an arterial occlusion and in association with numbness and coldness is due to ischemia. This explains the cause of the late pain present in 100 per cent of our cases. On the other hand, ischemia does not appear to be an adequate explanation for the early pain occurring at the level of the embolic occlusion. When pain at the onset was referred to the level of the occlusion, we have found that it preceded the onset of numbness and coldness. It was always of short duration, often lasting for only a few minutes, and was succeeded by prolonged distress or actual pain in the distal part of the affected limb developing in association with, or followed by, numbness and coldness in the same area. With the shifting of an embolic clot from the aortic bifurcation to the femoral artery, the patient may give a history of an initial pain in the back, later in the lower abdomen and, finally, in the groin over the femoral artery. The short duration of the pain at the level of the occlusion and the change in the location of the pain, with a change in the position of the embolic clot, occurring in certain cases make ischemia from occlusion of collateral vessels at the site of the main obstruction, as proposed by Lewis,¹ an unlikely explanation for the cause of this early pain, in our opinion. It appears to us that spasm at the site of the embolus, as first suggested by Seifert,² is a more probable cause for the early localized pain in complete embolic occlusion.

Occasionally patients with an embolic occlusion of the femoral artery, or occlusion even at a higher level, will complain of an early pain of maximum severity in the popliteal space, in the upper part of the calf, or in the foot. In one of our cases an acute pain developed in the foot, which preceded the onset of numbness and coldness. As this pain appeared when the patient was walking about and was promptly relieved by alternate suction and pressure treatment, it seems apparent that ischemia was the cause of this early, severe, local pain occurring distal to the site of the occlusion. This conclusion is in agreement with that of Lewis as to the cause of local severe pain occurring distal to the site of the embolic occlusion.

In two of our cases the patients complained of severe, temporary pain localized to the popliteal space, which developed subsequent to an embolic occlusion at a higher level. In one of these cases an embolus was removed from the common iliac artery, and later, at autopsy, an embolus at the bifurcation of the popliteal artery was found. One of us (D. G.³) has suggested that the acute, localized pain in the popliteal space probably followed occlusion of the artery from a fragment of the proximal embolus, local spasm being the probable cause of the pain.

In this connection, it is interesting that Ross⁴ has reported the relief of prolonged, acute pain in the popliteal space by excision of the occluded portion of the artery. The prolonged and localized character of the pain and its prompt disappearance following arteriectomy suggest local arteritis rather than ischemia as the causative factor for the pain in this instance.

In certain cases of embolic occlusion wherein a history of an acute early pain at the level of the occlusion is obtained, the pain, having remained localized to the site of the obstruction for a brief period, later spreads down the limb. When such a pain develops, it is of short duration and like the early localized pain precedes the development of numbness, coldness, and distress or pain arising in the extremity distal to the occlusion. At the present time no adequate explanation can be offered for the cause of this pain which spreads distally from the level of the occlusion.

The occurrence of an early as well as a late type of pain in many cases of acute arterial occlusion is of diagnostic importance. In our experience a history of an initial pain at the level of the occlusion is diagnostic of occlusion from embolism and never occurs in spontaneous thrombosis. The thrombotic attack, as a rule, begins with numbness and coldness, and the pain which follows these premonitory symptoms arises distal to the level of arterial closure. Like the late pain of embolism, it would appear to be of ischemic causation.

TREATMENT

The purpose of treatment of acute arterial occlusion is the early re-establishment of the blood supply of the affected limb. This may result from the development of an adequate collateral circulation or, in patients with occlusion from embolism, from removal of the obstruction by operation. Arteriotomy provides the only means whereby the obstruction may be removed and the continuity of the occluded artery restored. This is only possible in acute arterial occlusions due to emboli.

The satisfactory immediate results following early operation in a considerable percentage of cases of acute embolic occlusion made embolectomy the accepted method of treatment in this condition. Our experience with eleven cases treated by embolectomy has not been satisfactory. In the evaluation of this method of treatment it would appear that too much stress has been laid on the satisfactory results that may follow early operation and too little attention paid to the late results following embolectomy and to the percentage of spontaneous recovery of the circulation following acute arterial occlusion.

In connection with embolectomy we would like to point out that spontaneous recovery is not uncommon (Table I). In one case of complete occlusion of the aortic bifurcation spontaneous recovery occurred. Some months later this patient died of ventricular fibrillation, and at

TABLE I
IMMEDIATE RESULTS IN TREATED AND UNTREATED CASES OF EMBOLISM OF THE LARGE PERIPHERAL ARTERIES*

SITE OF EMBOLUS	FREQUENCY	PER CENT	RESULTS WITH TREATMENT				RESULTS WITHOUT SPECIAL TREATMENT†		OUTCOME UNCERTAIN AT DEATH‡
			CIRCULATION RESTORED		GANGRENE		CIRCULATION SPONTANEOUSLY RESTORED	GANGRENE	
			PAVAEX THERAPY	EMBOLIC-TOMY	PAVAEX THERAPY	EMBOLIC-TOMY			
Popliteal	16	24.6	3	0	2	0	3	6	2
Femoral	20	30.8	2	0	1	0	5	6	2
Hine	6	9.2	0	1	3	1	0	0	1
Aortic bifurcation	9	13.9	2	2	0	1	1	2	1
Brachial	5	7.7	0	1	0	0	3	0	1
Axillary	6	9.2	0	2	0	0	3	0	1
Subclavian	3	4.6	0	0	0	0	3	0	1
Total	65	100.0	7	6	6	6	16	14	10
			(10.8%)	(9.2%)	(9.2%)	(9.2%)	(24.6%)	(21.6%)	(15.4%)

*Embolec occlusion of the large arteries of the upper and lower limbs occurred 65 times in 31 cases. 10 of extremities involved. No treatment asked for.

*Embolus occlusion of the large arteries of the upper and lower limbs occurred 65 times in 41 cases. The analysis is based on the total number of extremities involved.

†No treatment aside from heat to the body.

‡Death as result of congestive heart failure or cerebral embolism occurred within twenty-four hours of the embolic attack. In three instances suction and pressure treatment was given.

autopsy complete obliteration of the aorta at the bifurcation was found. In a series of thirty-six cases of complete occlusion, of the common femoral artery in twenty and of the popliteal artery in sixteen, spontaneous recovery of the circulation occurred in approximately 20 per cent of each group. Among fourteen cases of complete occlusion of the arteries of the upper extremity, seven recovered without any special form of treatment; three recovered following embolectomy; and four died from the primary disease within a few hours of the onset of occlusion, before it was possible for recovery of the circulation to occur. When acute embolic occlusion of the arteries of the upper extremities occurs in patients not suffering from severe failure of the general circulation, spontaneous recovery would appear to be the rule rather than the exception, and one would question, therefore, the need for embolectomy or for any other special form of treatment in cases of embolism of the large arteries of the upper extremity.

Pearse⁵ found that 52 per cent of 282 cases died within one month after operation, the chief cause of death being the primary disease and, to a lesser extent, recurrent emboli. In analyzing the operative results in 382 cases in Sweden, Nystrom⁶ found that the late result was satisfactory in but 86, or 22.5 per cent of cases. Strömbeck,⁷ who followed up 61 of these 86 patients, found one-third of this number living after five years and only three patients who were able to return to a gainful occupation.

These findings, which are in agreement with our own experience, go to show that the primary disease, and not the immediate restoration of the peripheral circulation, is the important factor in determining the late prognosis in acute arterial occlusion.

As the primary disease plays such an important rôle in both the causation and the prognosis of acute arterial occlusion from thrombosis and embolism, treatment directed toward the early restoration of the circulation by measures other than embolectomy would seem to be indicated. This has now been made possible through the introduction of alternate suction and pressure treatment by Herrmann and Reid⁸ and Landis and Gibbon.⁹ Alternate suction and pressure therapy has the advantage of being applicable to cases of thrombosis as well as of embolism, and in the treatment of the latter is not limited by the duration of the occlusion. We have treated ten consecutive cases of arterial embolism with alternate suction and pressure. The results have been extremely encouraging. In all cases the occlusion was of the main arteries of the lower extremities. In five of the ten cases the circulation of the affected limbs was restored. In four of the five successful cases, treatment was begun within five hours of the embolic attack. Two were cases of embolus of the aortic bifurcation; one was a case of embolus of the left common femoral and right popliteal arteries; in another the embolus was located in the common femoral artery; and in the fifth it was in the popliteal artery and was

associated with extensive secondary thrombosis. In two of the cases of bilateral occlusion, all pulses returned to both lower extremities within four months of the occlusive attack. In five cases this treatment was ineffectual. Two patients, both with occlusion of one popliteal and of the opposite femoral artery, were moribund when treatment was started, and at the time of death the outcome in respect to the limbs was uncertain. Another, with a popliteal embolus, had subacute bacterial endocarditis. The fourth patient had an embolus of the common iliac artery. And the last patient had bilateral emboli of the external iliac arteries. In three of the five failures, treatment was instituted twenty-four hours or more after the embolic attack, and in two during the first ten-hour period.

In four cases of spontaneous thrombosis, alternate suction and pressure failed to improve the circulation of the limb. Two of the four patients had thrombosis of the popliteal artery; one had thrombosis of the aortic bifurcation and of one common iliac artery; and the fourth had thrombosis of the superficial femoral artery. In two the involved extremities were gangrenous when treatment was started. All had advanced coronary disease and congestive failure. Amputation was necessary in three of the four cases, and death while in hospital was the outcome in every instance. The character of these cases was such as to constitute an unfair test for suction and pressure treatment. In the hands of others,^{10, 11} it has produced encouraging results and it would appear to be a definite advance in the treatment of spontaneous thrombosis.

An embolus may initiate spasmodic contraction of the arterial wall in the region of the vessel when the clot is arrested. It is probable that this vasomotor reaction affects the anastomotic pathways as well as the main arterial channel. For this reason Denk¹² proposed the use of antispasmodic drugs and in six of ten cases of embolism achieved good results with intravenous eupaverine hydrochloride. Similarly favorable results were reported by de Takats¹³ in two cases, and by Allen and MacLean¹⁴ in one case. We have used papaverine hydrochloride in doses of $\frac{1}{6}$ to $\frac{1}{2}$ grain (0.166 gr. to 0.5 gr.) intravenously every four hours to supplement suction and pressure therapy in three cases of embolism. Because we wished to evaluate the latter form of treatment, the drug was withheld in all three until the recovery process was well advanced. We, therefore, have no data concerning the results of this other conservative form of treatment.

SUMMARY

In embolism of the large peripheral arteries, two distinct types of pain may arise. There may be pain at the level of the occlusion of short duration but of maximum severity at the onset of the attack. It merges into and is replaced by late pain of ischemic causation which arises in the distal part of the affected extremity. The late pain differs

greatly in character from the early distress, and it is felt that the early pain is probably due to arterial spasm initiated by the embolus. In thrombosis of the large arteries, similar early pain does not arise.

Attention has been called to the frequency of spontaneous recovery of the circulation in acute embolic occlusion of the larger arteries of the upper extremity.

The final result of treatment of embolic occlusion is largely determined by the severity of the associated primary disease. The results of suction and pressure therapy, in our experience, surpass those of embolectomy. We would agree with Herrmann and Reid and others that more conservative methods of therapy are indicated in the treatment of acute arterial occlusion. It is suggested that the ideal method of treatment for acute arterial occlusion is a combination of the nonoperative methods, namely: suction and pressure therapy, antispasmodic drugs, and heat to the body.

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THE ELECTROGRAM OF CARDIAC MUSCLE

II. THE LENGTHS OF THE STAGES OF ACTIVITY*

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I

BY MEANS of the concepts developed in the previous paper,¹ it was possible to predict with considerable exactness the shape of electrograms obtained under various circumstances, but, in order not to complicate unduly that argument, the means of obtaining measurements of the duration of the excitation process from the recorded curves was not discussed. The measurements which are needed are: first, the time during which the muscle is in any stage of activity; second, the time during which the muscle is fully active and the length of the periods during which its activity is increasing and decreasing; third, the velocity with which the process spreads along the muscle. Information about two other matters is also desirable: first, a measure of the intensity of full activity (of two muscles both of which are fully active the manifestations of activity may be of much greater magnitude in one than in the other) and, second, the nature of the rate at which activity increases or decreases. This rate may be constant or a function of the stage of the process (activity may increase rapidly at first and more slowly later on or vice versa).

The last two items are complicated problems requiring a knowledge of the three first mentioned for their solution, and will not be dealt with in this communication. Of the first three, the first can be derived from the second, and methods for determining the third are well known. The concern of this paper will be, therefore, a description of the means of ascertaining the duration of the stages of increasing, full, and decreasing activity from a suitably recorded electrogram. Certain assumptions in the previous paper about the lengths of these processes will then be checked, and finally, since a somewhat different approach to the problem is necessary, the correctness of the method of analysis previously used can be tested. The experiment which is introduced serves the double purpose of illustrating the application of the concepts theoretically derived and of testing their validity.

II

Muscle does not become active instantaneously. The active process spreads with a given velocity so that one length of muscle will be be-

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coming active, another will be fully active, and a third will be regressing from the active state. The lengths which are in transition are the distances over which the potential difference which exists between resting and active muscle must be distributed. It is possible to represent the potential difference either by a chain of doublets distributed along the transitional region or by a single positive and a single negative pole located at its beginning and end, respectively. Conversely the length of the doublet chain or the distance apart of the positive and negative poles measures the length of the transitional region. *A B C D* (Fig. 1A) represents an excitation process which travels over a muscle fiber from left to right, *A B*, *B C*, and *C D* constituting the stages of increasing, full, and decreasing activity, respectively. *E* is an electrode. It has been shown¹ that the transitional process gives rise to a train of doublets and that such a train is equivalent to a single positive and a single negative

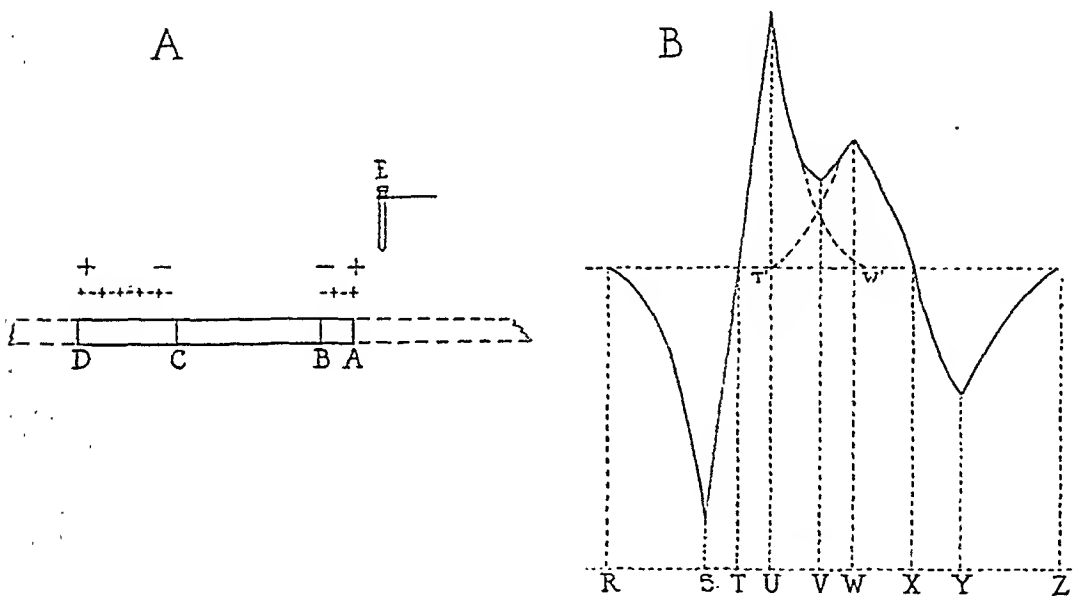


Fig. 1.—A. An electrode *E* is represented in close proximity to a strip of muscle along which the excitation process *A B C D* is passing from left to right. From *A* to *B* the muscle is increasing in activity, from *B* to *C* it is fully active, and from *C* to *D* the muscle is decreasing in activity. The potential differences between active and resting muscle which must be distributed over the transitional regions are represented both as chains of doublets (pairs of positive and negative poles infinitely close together) and as dipoles (single positive and single negative pole separated by a finite distance).

B. An hypothetical electrogram is shown such as would be produced by the passage of the potential differences depicted in A under the electrode. *R S T U W'* is the accession deflection; *T' W X Y Z* is the regression deflection.

S and *U* indicate the arrival of *A* and *B*, respectively, beneath the electrode and *W* and *Y* the arrival of *C* and *D* respectively.

From *T'* to *W'* the electrogram is produced by electrical effects resulting from both the accession and regression of activity.

pole separated by its length. If this latter concept is used the accession* deflection of the electrogram is written by the positive and negative poles located at *A* and *B*, respectively, as they pass under the electrode. The maximum positive effect may be expected to occur, therefore, when the

*It was shown in the previous paper that the electrogram is the sum of two diphasic curves. The first and more rapid, the result of electrical changes accompanying the accession of activity, is called the accession deflection; the second and slower, caused by electrical changes which accompany the regression of activity, is called the regression deflection.

positive pole is immediately beneath the electrode E , and the maximum negative effect when the negative pole is in this position. $S U$ (Fig. 1B) measures accordingly the duration of the stage of increasing activity and $W Y$ the stage of decreasing activity. Since U signals, furthermore, the end of the stage of increasing activity and W the beginning of decreasing activity, the interval $U W$ measures the duration of full activity.

In this simple analysis no account has been taken of the fact that as the forward member of the dipole approaches the electrode, the effect of the hinder one is also increasing. While the effect of the forward member is maximum when it is directly beneath the electrode, this effect is counterbalanced to a certain extent by the proximity of the hinder member. It is consequently not perfectly clear that the resultant effect will be maximum when the forward member is beneath the electrode, particularly if the two members are close together. Wilson, Macleod, and Barker² have, in fact, shown that when the two members of a dipole are close together the maximum and minimum points of the curve do not occur exactly at the time when the corresponding members of the dipole are directly beneath the electrode. It is necessary, therefore, to learn whether the intervals between the maximum and minimum points of the curve measure the stages of activity with a reasonable degree of accuracy. The most satisfactory way to solve this problem is to derive a mathematical expression for the potential of the electrode at any moment and to ascertain analytically its maxima and minima. For this purpose it is convenient to deal with trains of doublets. Since both accession and regression deflections are produced by trains of doublets which differ only as to length and polarity, it is necessary to consider only three phases of the problem: (a) when the doublet train is shorter than the muscle, (b) when it is longer, and (c) when it is of equal length.

A muscle fiber, an electrode (E), and a short train of doublets (Fig. 2A) illustrate the conditions existing when the doublet train is shorter than the muscle. The long axis of the muscle fiber coincides with the x axis in a system of rectangular coordinates (Fig. 2B). The tip of the electrode is at a distance b from the origin on the y axis. x represents the position of the head of the train of doublets supposed to be travelling over the muscle from left to right, and L is the length of the doublet train. For the sake of simplicity the velocity V with which the doublet train travels is assumed to be unity, so that a unit of time and a unit of distance are represented by equal intervals on the graph. If then, the effect of any doublet upon the electrode is given by the formula

$$P = \frac{\mu \cos \theta}{R^2}, \text{ the effect of the whole train will be}$$

$$1. \quad P = \mu \int_{x-L}^x \frac{-x'}{(x'^2 + b^2)^{3/2}} dx' = \frac{\mu}{\sqrt{x^2 + b^2}} - \frac{\mu}{\sqrt{(x-L)^2 + b^2}}$$

This expression defines the effect upon the electrode for any position of the doublet train so long as all of it is on the muscle fiber. A graph of this function is also shown in Fig. 2B. To ascertain the maximum and minimum values of this function, it is necessary only to differentiate it with respect to x and equate the derivative to zero. This gives the equation

$$2. \quad D_x P = \frac{\mu (x - L)}{[(x - L)^2 + b^2]^{\frac{3}{2}}} - \frac{\mu x}{(x^2 + b^2)^{\frac{3}{2}}} = 0.$$

Obviously neither $x = 0$ nor $x = L$ is a root of this equation.

Consequently the maximum and minimum values of the function do not accurately signal the arrival of the head and tail of the doublet train,

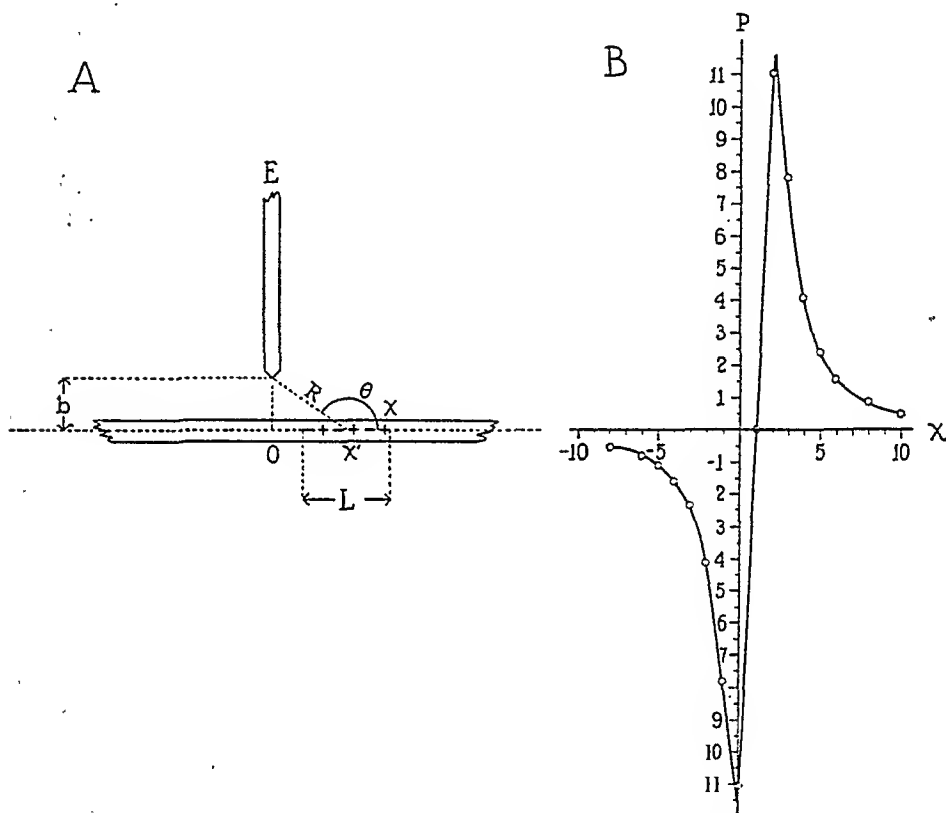


Fig. 2.—A. A short train of doublets travelling along a muscle strip is shown in relation to the exploring electrode E . L is the length of the doublet train; b the distance of the tip of the electrode from the muscle; x the distance of the head of the doublet train from the origin 0 ; x' the distance of any doublet in the train from the origin; R the distance of the doublet at x' from the tip of the electrode; θ the angle between R and the line along which the doublets are travelling.

B. The graph of the function is plotted in which

$$P = \frac{\mu}{\sqrt{x^2 + b^2}} - \frac{\mu}{\sqrt{(x-L)^2 + b^2}}$$

i.e., the graph of the potential change produced in E by the passage of the doublet train along the muscle strip.

respectively, beneath the electrode, and the statement first made, that SU (Fig. 1) measures the duration of the phase of increasing activity, is not strictly correct.

During the regression of activity the signs of the doublets are reversed and the train is represented as longer than the muscle over which it travels (Fig. 3). It is simplest to consider the problem in three parts:

first, the period during which the head of the doublet train is in the act of progressing over the muscle; second, the period during which the muscle is completely covered by the doublet train; and third, the period during which the tail is passing over the fiber. Fig. 3A represents the first of these situations. The symbols have the same notations as before. A and B are the abscissae of the ends of the muscle strip.

In this case the potential of the electrode is defined by the equation

$$3. \quad P = \mu \int_A^x \frac{x'}{(x'^2 + b^2)^{3/2}} = \frac{\mu}{\sqrt{A^2 + b^2}} - \frac{\mu}{\sqrt{x^2 + b^2}}.$$

This expression defines the potential of the electrode for the interval $X = A$ to $X = B$ or from the time of the first beginning of activity till the head of the active process reaches B . During this period the curve will reach its maximum value when $X = 0$, for $D_x P$ equated to zero gives the equation

$$4. \quad D_x P = \frac{-\mu x}{(x^2 + b^2)^{3/2}} = 0.$$

Obviously 0 is a root of this equation.

During the second stage (Fig. 3B) the potential of the electrode remains constant at the value it attained when the doublet train reached B since, for every doublet that passes off at B , one comes on to the strip at A . A constant relationship is therefore maintained between the doublets to either side of the electrode. Whether the potential of the electrode is zero, negative or positive, depends on whether the absolute value of A is equal to, greater than, or less than, that of B . The potential of the electrode is given by the equation

$$5. \quad P = \frac{\mu}{\sqrt{A^2 + b^2}} - \frac{\mu}{\sqrt{B^2 + b^2}}.$$

This expression defines the potential of the electrode for $[L - (B - A)]$ V seconds.

During the final period x represents the position of the tail of the doublet train (Fig. 3C). The potential of the electrode is expressed by the equation

$$6. \quad P = \int_x^B \frac{x'}{(x'^2 + b^2)^{3/2}} = \frac{\mu}{\sqrt{x^2 + b^2}} - \frac{\mu}{\sqrt{B^2 + b^2}}.$$

The duration of this stage is of course equal to that of the first. The curve will reach its minimum value, furthermore, when $X = 0$ for $D_x P$ equated to zero gives

$$7. \quad D_x P = \frac{\mu x}{(x^2 + b^2)^{3/2}} = 0,$$

and zero is a root of this equation.

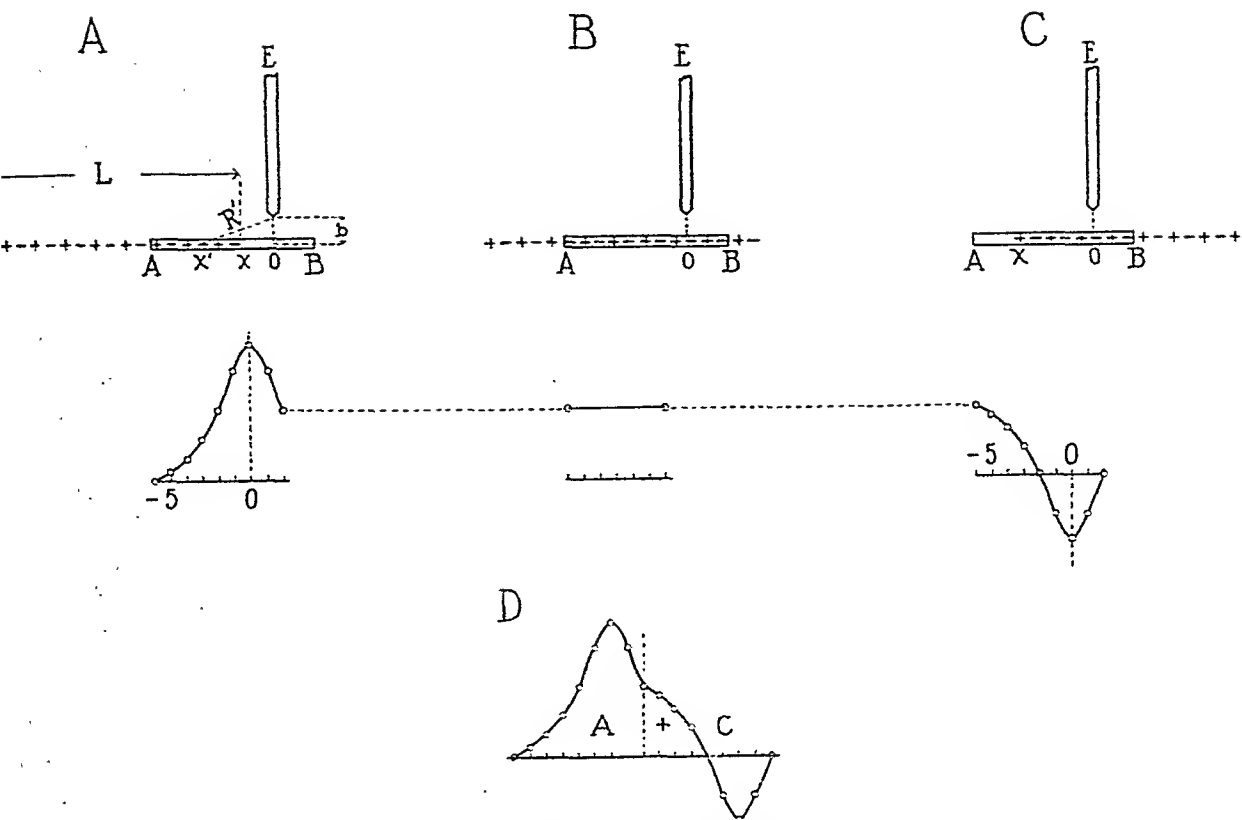


Fig. 3.—A. A short strip of muscle is represented over which a train of doublets longer than itself is travelling from left to right in relation to an exploring electrode *E*. *b* is the distance of the tip of the electrode from the muscle; *AO* the distance of the left end of the muscle from the origin 0; *OB* the distance of the right end from 0; *XO* the distance of the head of the doublet train from 0; *X'O* the distance of any doublet that is on the muscle from 0; *R* the distance of the doublet at *X'* from the tip of the electrode. Beneath the diagram of the muscle strip and the electrode is a graph of the function:

$$P = \mu \left[\frac{1}{\sqrt{A^2 + b^2}} - \frac{1}{\sqrt{X^2 + b^2}} \right]$$

i.e., a graph of the potential change produced in *E* by the passage of the doublet train onto the muscle.

B. The muscle strip is represented during the period when it is completely covered by the doublet train. The potential of *E* remains constant during this period because for every doublet that passes onto the fiber at *A*, one passes off at *B*. The potential of *E* during this period is

$$P = \mu \left[\frac{1}{\sqrt{A^2 + b^2}} - \frac{1}{\sqrt{B^2 + b^2}} \right]$$

Below is a graph of the potential of *E* during this period connected by a dotted line with the graph of the preceding period.

C. The muscle strip during the period that the doublet train is passing off the fiber. *X* now indicates the position of the tail of the doublet train. Below is the graph of the function

$$P = \mu \left[\frac{1}{\sqrt{X^2 + b^2}} - \frac{1}{\sqrt{B^2 + b^2}} \right]$$

i.e., the graph of the change of the potential of *E* caused by the passage of the doublet train off the fiber. The preceding graphs are connected with it by a dotted line. By connecting these three segments together the complete graph of the electrical effect of the passage of the doublet train over the fiber is obtained.

D. The graph of the effect upon the electrode of the passage of a train of doublets equal in length to the fiber; sections *A* and *C* are connected but *B* is omitted.

Therefore, when the doublet train is longer than the muscle over which it travels, the maximum and the minimum peaks of the electrogram accurately signal the arrival of its head and tail, respectively, beneath the electrode. This is also true when the length of the train is equal to that of the muscle, for under these circumstances the second part of the analysis is simply omitted (Fig. 3D). In other words the central flat portion of the curve disappears.

Although derived in a different way, equation 1 is of the same form as the equation which Wilson, Macleod and Barker² obtained in their discussion of linear excitation, so that it is permissible to make use of their reasoning in regard to the maxima and the minima of the function. They showed that in general the interval between the maximum and the minimum peaks of the curve is greater than that which separates the positive and negative elements of the dipole, and the greater the distance between the tip of the electrode and the muscle (b) the greater is the disparity. Their reasoning was based upon the fact that when the two elements of the dipole are very close together (when it approximates a doublet³) the interval between the maximum and minimum peaks is dependent upon b (distance from electrode tip to muscle) alone. When this fact is taken in conjunction with the demonstration which has just been made, that when the length of the train of doublets or the distance which separates the elements of the dipole is equal to or greater than the length of the muscle it is accurately measured by the interval between the maximum and the minimum peaks of the electrogram regardless of the value of b , it is logical to conclude that the greater the interval (if this is less than the length of the muscle) between the elements of the dipole, the more accurately this interval is measured by that between the maximum and minimum peaks of the electrogram. When b is small and L is by comparison large, no appreciable error is introduced, therefore, by using the interval between the peaks of the electrogram as a measure of the length of a transitional stage, even if this stage is shorter than the muscle. What error there is will be greater in the case of the stage of increasing activity, but even in this case it will not be great for as will be shown subsequently, the length of this stage is several millimeters, whereas the distance of the electrode from the muscle is probably less than 0.1 mm.

If the graph of equation 1 is compared with the first part of the theoretical electrogram (Fig. 9 or 10 of the foregoing paper), it will be seen that the two are of identical shape. If the graphs of equations 3, 5, and 6 are connected seriatim, they also will be found to be identical with the graph of the effects of the regression of activity (Fig. 11 of the previous article). Without further demonstration it may be stated,

³For convenience the term *dipole* is used to designate a positive and negative pole separated by a finite distance in contradistinction to a doublet, the positive and negative poles of which are infinitely close together. A dipole is equivalent to a chain of doublets.

therefore, that any of the theoretical electrograms illustrated in the previous paper may be reproduced by combining the graphs of appropriate mathematical expressions. As it happened, the shapes of the theoretical electrograms were arrived at first by means of this sort of mathematical analysis. The graphic method was devised later because under certain circumstances the mathematical procedure becomes very cumbersome. Under the simple circumstances that have been dealt with so far, the mathematical analysis can be used as satisfactorily as the graphic one. But if the problem is complicated, as for instance, if the duration of a stage of activity were different at one end of a muscle from that at the other, the mathematical analysis would become too complex to be useful. In the graphic method it would then be necessary only to make the corresponding rectangles of different dimensions. It is possible also that the graphic method gives a clearer insight into the mechanisms whereby the electrogram is produced. Because of its greater flexibility and clarity the graphic method is in general to be preferred, but it is difficult by means of it to demonstrate the significance of the maximum and minimum points of the curve. For this reason and because the mathematical analysis is an excellent check on the validity of the graphic method, it has been briefly discussed.

III

To illustrate the application of the concepts which have been developed and to test their validity, an experiment was performed. The apparatus and arrangements were similar to those employed in the previous investigations except that two simultaneous records were taken, one from the central region of the auricle and one from a point near the auriculo-ventricular junction. It was possible in this way to learn the form of the curves from these two points and further to ascertain the velocity of transmission of the impulse. In Fig. 4A is such a pair of curves. They resemble in form the curves taken from similar positions in the previous paper (Fig. 10C and 11C). Without moving the electrodes, another record was taken after warming the heart by flushing it with warm saline solution (Fig. 4B). The accession deflections before and after warming are similar. The upward peak of the curve from the central portion of the auricle after warming (Fig. 4B, a_2) is slightly lower than the corresponding peak of the curve at room temperature (Fig. 4A, a_2) but the general form of the two is the same. This distortion probably results from the fact that the auricle was not warmed symmetrically. The regression deflections are, however, markedly different. In the set taken at room temperature, they have the forms that are expected (previous paper Figs. 10 and 11). In the curve from the central portion of the auricle the first upward phase (r_1) is concealed within the accession deflection, the flat portion coincides approximately with the isoelectric line and is followed by the final downward deflection (r_2). In

the curve from the vicinity of the auriculoventricular junction, the first upward deflection (r_1) is again concealed in the accession deflection, the flat portion is above the isoelectric line and is followed by a downward deflection (r_2), which is smaller than that of the curve from the center. After warming, the regression deflection of the curve from the central region becomes definitely diphasic with no flat central portion, and the two phases are approximately equal. The curve from the auriculoventricular junction also becomes diphasic, but the upward phase (r_1) is much larger than the downward (r_2). After warming, both summits of the regression deflection (r_1 and r_2) are visible, and the distance be-

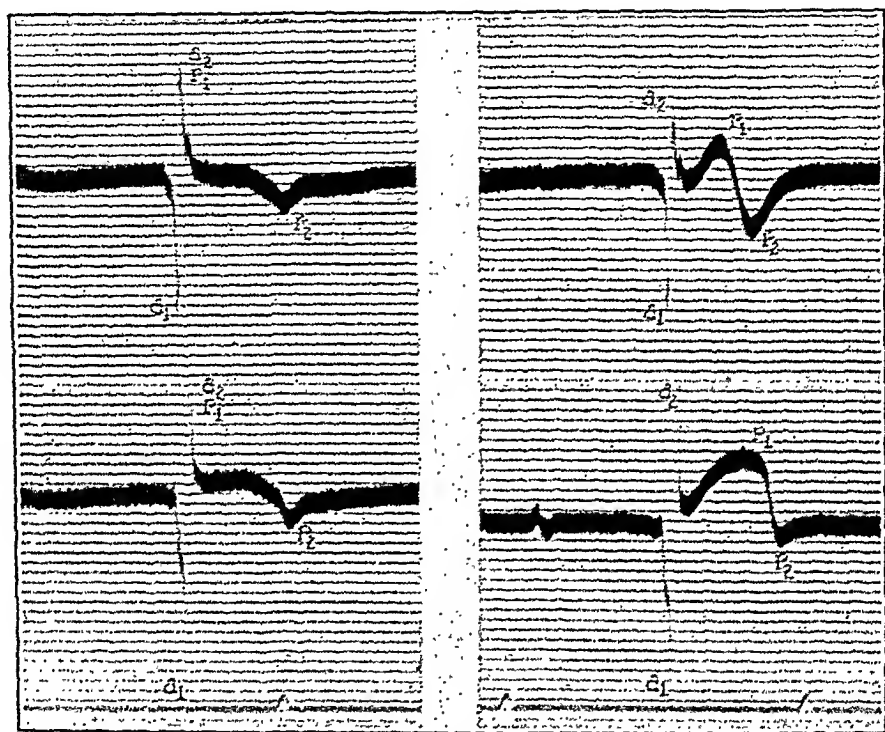


FIG. 4.—A. A pair of electrograms is shown taken from the anterior surface of a frog's auricle at room temperature. The upper curve was derived from the central region of the auricle and the lower one from a point 5 mm. nearer the auriculoventricular junction; a_1 and a_2 are the downward and upward peaks of the accession deflection; r_1 and r_2 are the upward and downward peaks of the regression deflection. r_1 is concealed in a_1 ; a_2 . The flat portion of the upper curve which connects r_1 and r_2 coincides approximately with the isoelectric line. The corresponding part of the lower curve is above the isoelectric line.

B. A pair of electrograms is shown taken from the same points as in A after the preparation was warmed. r_1 is now visible in both curves, and the flat portion has disappeared. The time marked indicates seconds.

tween them, and therefore the duration of the phase of decreasing activity, can be easily measured. In the case of the curves taken at room temperature, the measurement of the duration of the regression process is necessarily inaccurate, but a very good approximation to it can be made by assuming that the summit of the upward peak is at the center of the accession deflection. These measurements are given in Table I.

Since the time at which the rapid upstroke of the accession deflection crosses the isoelectric line corresponds to the time at which the center of

the stage of increasing activity is beneath the electrode, the interval between the crossing of the isoelectric line in the top curve and the crossing in the bottom curve represents the time necessary for the impulse to travel from one electrode to the other. From this measurement and the distance between the electrodes the velocity with which the process of activation travels can be obtained. This velocity increases with increase in temperature.

In practice the accurate measurement of the velocity is attended with considerable difficulty. The velocities given in Table I are corrected as far as possible. But since the error in measuring the distance between the electrodes is approximately 10 per cent, they are inaccurate to this extent. Great accuracy is not essential, however, for the purposes of the present argument.

TABLE I

	VELOCITY OF IMPULSE (MM./ SEC.)	DURA- TION OF ACCES- SION PROCESS (SEC.)	DURA- TION OF REGRES- SION PROCESS (SEC.)	DURA- TION OF FULL AC- TIVITY (SEC.)	LENGTH OF ACCES- SION PROCESS (MM.)	LENGTH OF REGRES- SION PROCESS (MM.)	LENGTH OF PHASE OF FULL AC- TIVITY (MM.)
Room temperature	166	0.015	0.33		2.5	55	
After warming	218	0.015	0.11	0.17 to 0.20	3.3	24	37 to 44

One further measurement should be recorded, namely, the length of the auricular muscle from the sinus venosus to the auriculoventricular junction. Making this measurement is difficult when the heart is in place because its surface is curved and part of it is inaccessible or accessible with difficulty. Only a rough estimate can, therefore, be made. It was from 20 to 25 mm.

IV

The most striking fact in Table I is the very marked disproportion between the lengths of the accession and regression deflections in the curves taken at room temperature. The regression process is more than twenty times as long as the accession process. The duration of full activity cannot be ascertained because the preliminary upward deflection (r_1) of the regression process is concealed within the accession deflection, but its duration must be very brief. It will, therefore, be seen that the conditions assumed formerly¹ to be present are justified. The concept then proposed was that the excitation process consists (1) of a brief stage during which activity is increasing, (2) of a very brief period of full activity, and finally (3) of a long stage of decreasing activity. The assumption that the regression process is usually longer than the muscle over which it travels is also confirmed. The distance travelled by the impulse in this experiment was 20 to 25 mm. (distance from sinus

venosus to ventricle along the anterior surface of auricle) whereas the length of the regression process was 55 mm.

An essential point in the conception of the regression deflection as developed in the present study and in the preceding is that it is a diphasic process. It has, however, been necessary to assume that the first of the regression phases is usually concealed within the larger accession deflection. That this is a possible state of affairs is obvious, but it may be well to summarize the evidence for its probability. In the first place, a theory which requires the existence of an upward phase for the regression process satisfactorily explains the displacement of the flat portion of the electrogram above and below the isoelectric line as well as the shape and size of the terminal deflection. Second, under certain circumstances, such as the application of heat, the regression deflection becomes obviously diphasic (Fig. 4B and in the previous paper, Fig. 9).

The use of heat to bring out the diphasic character of the regression deflection resulted from reasoning in the following manner. Since under ordinary circumstances the upward phase of the regression deflection is small as compared with the accession deflection, it seemed probable that if its amplitude could be increased in some way, evidence of its existence might be obtained. It was observed that increase in temperature decreases the duration of the regression process, and for theoretical reasons* it was believed that a decrease in duration should be accompanied by an increase in magnitude. The curves in Fig. 4B fulfill this prediction. The upward phase is now easily seen in the curves from both portions.

The measurements in Table I indicate that after warming the heart the length of the regression process is equal to that of the course over which it travels. Under these circumstances the flat central portion should disappear (Fig. 3D), and this deduction too is borne out by the experimental curves. That the stage of full activity would be increased could not have been predicted, for no method of analysis capable of bringing out this fact was hitherto available. What its significance may be will require further investigation. This ability to predict with some accuracy the behavior of the electrogram under varied circumstances would seem to be added evidence for the validity of the concepts developed.

SUMMARY

1. A method for measuring the stages of increasing, full, and decreasing activity of cardiac muscle from suitably recorded electrograms is described and the critique of the method discussed.

*It has been shown that the electrical activity of a minute segment of muscle can be represented by a rectangle whose height is proportional to its magnitude and whose length is proportional to its duration. If it is assumed that the difference of potential between active and resting muscle is always the same, it must follow that the area of the rectangle which represents the electrical effect must remain constant. While any reduction in the length of the regression process will decrease the duration of the effect (length of the rectangle), this must be accompanied by a proportional increase in the magnitude of the effect (height of the rectangle) because the total potential difference between active and resting muscle is now distributed over a shorter stretch of muscle, and each muscle segment will contain a proportionally greater portion of it.

2. A mathematical analysis of the electrogram has been used to check a previously described graphic one.

3. Further evidence has been brought forth for the concept that the electrogram of cardiac muscle consists of two diphasic curves (an accession and a regression deflection) produced by potential differences distributed over that portion of the muscle which is undergoing transition from resting to active state and vice versa.

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THE VENTRICULAR DEFLECTIONS IN MYOCARDIAL INFARCTION

AN ELECTROCARDIOGRAPHIC STUDY USING ESOPHAGEAL AND PRECORDIAL LEADS*

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THE attempts to determine the sites of myocardial infarcts by the recognition of characteristic electrocardiographic curves started in 1928 when Parkinson and Bedford¹ demonstrated that there were two general types of curves obtained from patients who had suffered from coronary thrombosis. They called these the T_1 and the T_2 types. In the T_1 type there was upward displacement of the RS-T segment and inversion of T-wave in Lead I, while in Lead III the RS-T segment was displaced downward and the T-wave was sharply upright. In the T_2 type the RS-T segment was displaced upward in Lead III and downward in Lead I and the T-wave was inverted in Lead III and upright in Lead I. In the following year Barnes and Whitten² showed that the T_1 type was frequently associated with infarction of the anterior surface and apex of the left ventricle, i.e., in the distribution of the anterior descending branch of the left coronary artery, and the T_2 type with infarction of the posterior and basal part of the left ventricle, i.e., in the distribution of the posterior circumflex branches of both right and left coronary arteries. Gilchrist and Ritchie,³ however, among others, considered that localization by means of RS-T and T-wave changes was not infallible when they failed to obtain good correlation between the site of the infarct and the electrocardiographic pattern. Later Wilson and his associates⁴ found that a large Q-wave was usually present in Lead I in the T_1 or anterior type and a large Q-wave in Leads II and III in the T_2 or posterior type.

Further assistance in the localization of infarcts as well as diagnosis has resulted from the use of precordial leads and exploring leads. Wilson and his associates^{5, 6} theoretically and experimentally showed that part of the heart nearest the electrode shows a preponderating influence upon the form of the curve. Consequently⁷ in precordial leads the electrical activity of the anterior wall of the heart has a much greater effect on the form of the curve than the electrical activity of the posterior wall. In 1932 they⁸ showed two types of precordial curves associated with changes in QRS and T in coronary thrombosis. The first group showed an initial deflection of their curves which is

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upward and of large amplitude and not preceded by a downward deflection, as is ordinarily the case. The T-waves of this group may be negative. In the second group the initial deflection is usually downward and of large amplitude. The T-waves were sharply inverted. The former was associated with anterior wall infarction and the latter with posterior type of infarction. In the same year, however, Wolferth and Wood and their associates^{9, 10} were the first to show that precordial leads may display RS-T displacement as well as QRS and T-wave changes in coronary thrombosis when the standard curves are equivocal.

The failure of precordial leads to show striking abnormalities in cases of infarction of the posterior wall is probably due to the fact that the electrode lies at a considerable distance from the damaged area and the intervening healthy muscle exerts a major influence in writing the curve by virtue of its nearness to the electrode. Following the work of Lieberman and Liberson¹¹ in 1934 and of Brown¹² on the use of esophageal leads, we have attempted to study the electrical events occurring in the region of an infarct of the posterior ventricular wall by means of an electrode placed in the esophagus, i.e., in a position where close contact is obtained with the damaged area without the intervention of a large mass of healthy muscle. For comparison, we have taken precordial leads in cases of posterior infarction, as well as esophageal and precordial leads in cases of anterior infarction and in normal subjects. Records from one subject in each of these groups will be presented.

METHOD

After taking the three standard leads the precordium is explored, using a small German silver electrode (surface area of 1 sq. cm.) as the exploring electrode, and a central terminal attached to the arms and the left leg through three accurately standardized resistances each of 5,000 ohms (Wilson and his coworkers¹³) as the indifferent point. The galvanometer is connected so that relative electronegativity of the exploring electrode results in an upward deflection of the string in all records.* (The string sensitivity in all records was 1 cm. = 1 mv.) The points on which the exploring electrode is placed are as follows: on the fifth rib immediately to the right of the sternum (V_1), on the fifth rib immediately to the left of the sternum (V_2), in the fifth left intercostal space midway between the left lateral sternal line and the midclavicular line (V_3), in the fifth left intercostal space in the midclavicular line (V_4) and on the sixth rib in the left anterior axillary line (V_6).¹⁴ The potential variations of each extremity are then recorded by attaching the exploring wire (right arm) in turn to the electrodes already applied to the right arm (VR), the left arm (VL) and the left leg (VF), the left arm wire from the galvanometer being connected to the central terminal.¹⁴

Records are finally taken by the esophageal lead. The electrode is of German silver, of circular cross-section, 8 mm. in diameter by 20 mm. in length, and has slightly tapering ends. It is soldered to four strands of insulated copper wire enclosed in a rubber duodenal tube of the Relfuss type. The right arm wire of the

*When this paper was written, this was the conventional method of recording the laboratory potentials. The nomenclature proposed in Wilson's laboratory¹⁴ had not yet been adopted by the American and British Heart Associations.

galvanometer is attached to the esophageal electrode and the left leg wire to the same indifferent terminal as is used for the precordial leads. The pharynx is cocaineized and the electrode passed until it reaches a point 50 to 60 cm. from the incisor teeth, depending on the build of the patient. It is then drawn up 2.5 cm. at a time and records are taken at each interval until a point 25 to 30 cm. from the teeth is reached.

Brown has shown¹² that when the esophageal electrode lies in the region of the auricles characteristic P-waves are written which contain rapid upstrokes analogous to the intrinsic deflection of direct leads. These intrinsic deflections disappear when the electrode is passed below the auriculoventricular groove. Examination of the proximity of the esophagus to the posterior surface of the ventricles in the cadaver

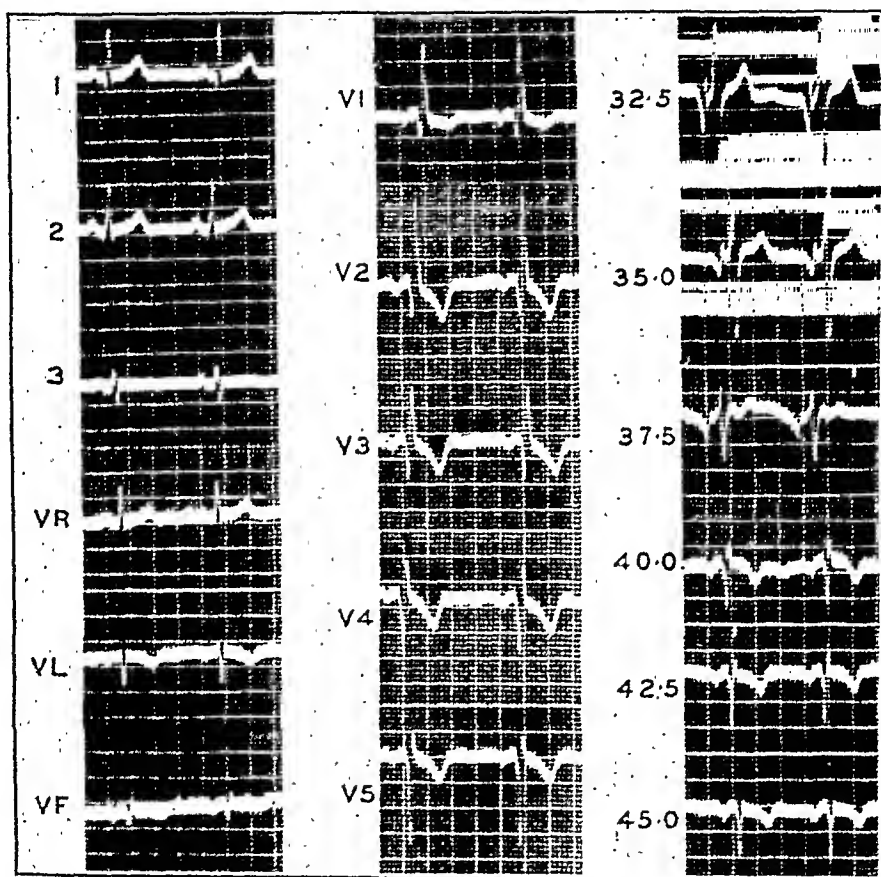


Fig. 1.—Normal subject.

Standard leads 1 2 3
Extremity potentials VR VL VF

Precordial leads V₁ V₂ V₃ V₄ V₅
Esophageal leads 32.5, 35, 37.5, 40, 42.5,
45 cm. from the incisor teeth.

(String sensitivity, 1 mv. = 1 cm. in this and the other records.)

shows that close contact is made with the base of the left ventricle, though there may be some divergence lower down. We have therefore selected those tracings obtained from points 5 cm. and more below the lowest level showing characteristic P-waves, as being from the posterior surface of the left ventricle.

RESULTS

1. *Normal Subject* (Fig. 1).—The standard leads show slight left axis deviation, probably due to the transverse position of the heart. This slight axis change is shown also by the presence of a major

downward deflection in the left arm potential curve.¹³ Otherwise the extremity potential curves are within the limits of normal set by Kossmann and Johnston.¹⁴ The precordial curves also fall within the normal limits established by these authors.

The esophageal tracings show that characteristic intrinsic auricular deflections are present in the curves taken at 35 cm. and at 32.5 cm. from the teeth. The ventricular deflection is composed of an initial summit followed by an approximately equal depression and a well-marked upright T-wave. The RS-T segment starts close to the isoelectric level but rises steeply into the T-wave. At 37.5 cm. the electrode probably lay close to both auricular and ventricular tissue since the initial ventricular deflection is similar in form to those recorded at higher levels, though the T-wave, diphasic in form, is intermediate between that seen at 35 cm. and that seen at 40 cm.

At and below 40 cm. the P-wave loses all sign of a sharp upstroke, showing that the electrode lay below the auricle and near the ventricular surface. The initial upright ventricular deflection seen at higher levels is replaced by a slight slurring of the major downward deflection, the latter being in turn succeeded by a small summit. The T-wave is directed downward, with the RS-T take-off practically isoelectric.

2. *Myocardial Infarction (Posterior Type).*—Case 1 (Fig. 2). *Standard Leads:* The electrical axis is normal. No Q-deflection is present in Lead I, Q_2 is 1 mm. and Q_3 is 25 per cent of that of the largest QRS deflection in any of the standard leads. Therefore Q_3 satisfies the criteria of Pardee.¹⁵ Neither Q_2 nor Q_3 is large enough to fulfill the conditions suggested by Durant,¹⁶ according to whom Q_2 should be at least 25 per cent of R_2 and Q_3 at least 50 per cent of the largest QRS in any lead. The RS-T segments in Leads II and III are markedly elevated and the T-waves in these leads are inverted, while in Lead I the RS-T segment is slightly depressed and the T-wave is upright. These abnormalities together with the clinical history and examination (see protocol) appear sufficient evidence on which to base a diagnosis of myocardial infarction of the posterior type.

Extremity Potentials: The right arm potential curve (VR) shows an initial upright ventricular deflection and a low voltage downward T-wave with slightly elevated RS-T take-off. In the left arm curve (VL) there is an initial depression followed by a summit, a considerably elevated RS-T segment and a downward T-wave, while the left leg curve (VF) shows an initial summit followed by a larger depression, a well-marked upright T-wave and a depressed RS-T interval. It will be noticed that Lead VL resembles Lead III in contour.

Precordial Leads: In these leads (particularly V_3 , V_4 and V_5) the ventricular complex is initiated by a deep downward deflection. The

RS-T segment is elevated and the T-wave is directed downward and of large size. These are in keeping with the abnormalities shown by the standard leads.

Esophageal Leads: At 42.5 and 37.5 cm. the presence of sharp rapid auricular deflections indicates that the electrode was close to the auricular surface. At 42.5 cm. the ventricular deflection does not differ in general form from those recorded from points lower down, but at 37.5 cm. it differs considerably. After a very small downward

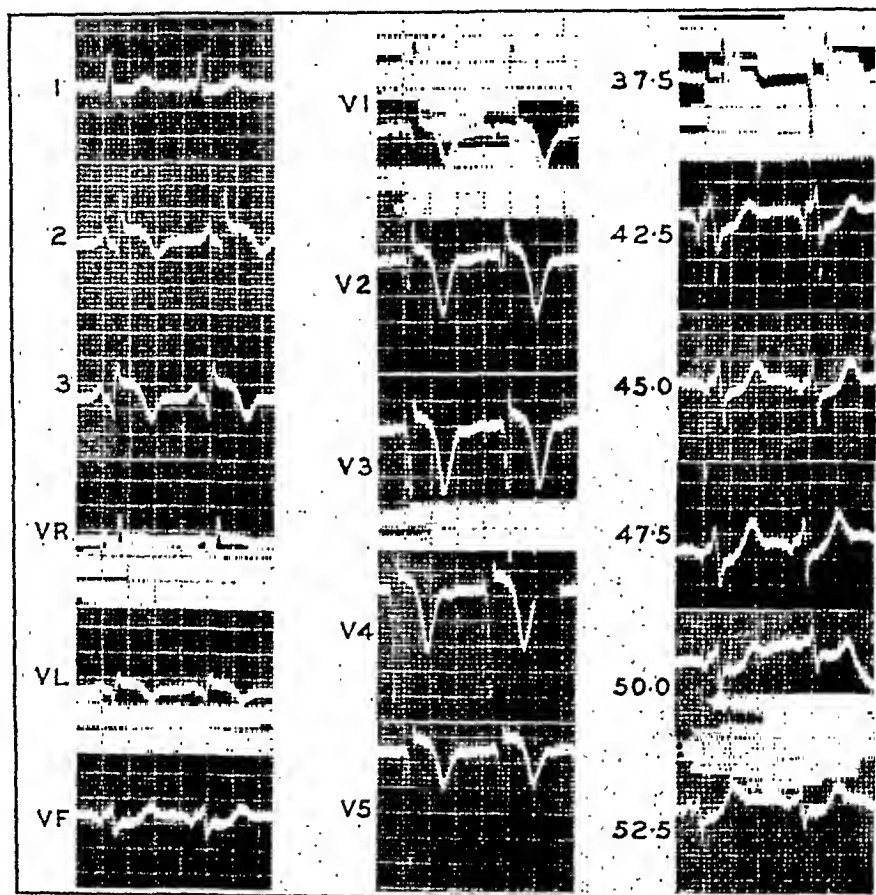


Fig. 2.—Case 1. Posterior myocardial infarction.

Standard leads 1 2 3
Extremity potentials VR VL VF

Precordial leads V₁ V₂ V₃ V₄ V₅
Esophageal leads 37.5, 42.5, 45, 47.5,
50, 52.5 cm. from the incisor teeth.

wave there is a relatively large upright deflection, smaller downward and upright waves, an elevated RS-T segment and an inverted T-wave.

The curves taken from juxtaventricular positions (namely 45 to 55 cm. from the teeth) show somewhat low amplitude of the initial ventricular deflection which begins with a small summit followed by a slow downward deflection, indicating relative electropositivity of the exploring electrode. After the next short but more rapid upward movement, which probably represents the intrinsic deflection, there

is a markedly depressed RS-T interval and an upright T-wave. By comparison there are marked similarities of the contours of these esophageal ventricular deflections to those of the left leg (VF).

3. *Myocardial Infarction (Anterior Type).*—Case 2 (Fig. 3). *Standard Leads:* The electrical axis is normal. Q-waves are present in Leads I and II. There is no Q-deflection in Lead III. The amplitude of Q_2 is 25 per cent of that of R_2 and the amplitude of Q_1 is greater than 1 mm. and more than one-fifth as large as the largest R-wave in any

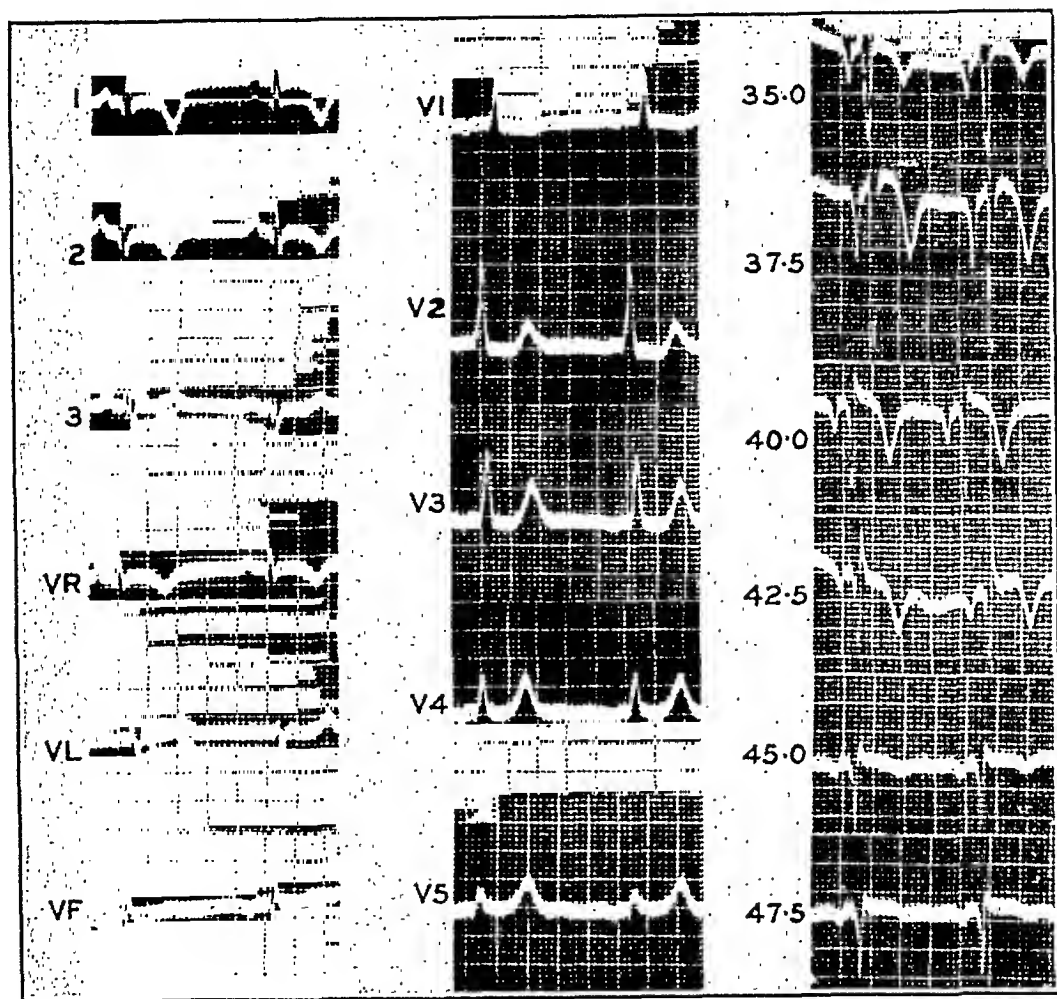


Fig. 3.—Case 2. Anterior myocardial infarction.

Standard leads 1 2 3
Extremity potentials VR VL VF

Precordial leads V₁ V₂ V₃ V₄ V₅
Esophageal leads 35, 37.5, 40, 42.5, 45,
47.5 cm. from the incisor teeth.

standard lead; R_1 is less than 5 mm. high. The RS-T segment is curved upward in Leads I and II and the T-waves are inverted, while in Lead III the RS-T segment is isoelectric and flat and the T-wave is upright. These abnormalities together with the clinical history and examination (see protocol) appear sufficient evidence on which to base a diagnosis of myocardial infarction of the anterior type. It is further noted that except for the presence of inverted T_2 , Durant's criteria¹⁶ for Q_1 T_1 type curves are satisfied.

Extremity Potentials: The right arm curve (VR) consists of a small initial downward, a well-marked upward, and another small downward wave, an inverted T-wave with a nearly isoelectric and upwardly convex RS-T take-off. The left arm curve (VL) shows small upward and larger downward deflections with an upright T-wave rising from the isoelectric level. In the left leg tracing (VF) there are again small upward and downward waves, but the latter are followed by a larger summit. The T-wave is small and upright and the take-off is isoelectric. VR resembles Lead I and VL Lead III.

Precordial Leads: These show an absence of the initial downward deflection. In V_2 the RS-T segment is slightly depressed but in other positions, isoelectric. In V_3 , V_4 , V_5 there is a downward convexity of this segment. The T-waves are upright from points to the left of the sternum. These abnormalities are consistent with the diagnosis of anterior infarction. In the routine apical lead records of this case made immediately and for some time after the acute episode, there was marked depression of the RS-T segment, in addition to the absence of an initial downward deflection and the presence of an upright T-wave.

Esophageal Leads: The characteristic auricular deflection appears at 37.5 and 35 cm. and is well marked until the 30 cm. level is reached. At these levels the ventricular complex, beginning with a small summit, is chiefly composed of a large downward wave. The RS-T segment is elevated and rounded and the T-wave directed downward. It is also observed that when the electrode lies over the lower part of the auricle and the upper part of the ventricle, between 37.5 and 42.5 cm., the T-wave is exceptionally deep.

In the curves obtained from juxtaventricular points (40, 42.5, 45, 47.5 cm.) the ventricular deflection consists of a well-marked downward swing with slight initial shurring followed by a summit, an elevated RS-T segment and a downwardly directed T-wave. The latter curves (45 and 47.5 cm.) somewhat resemble the leg lead (VF) except in amplitude.

DISCUSSION

Leads of the type used in this study are theoretically unipolar and represent the potential variations of the exploring electrode with respect to an indifferent central terminal, the potential of which remains at zero throughout the cardiac cycle. When the exploring electrode is placed in close proximity to the heart the resulting curve records, more or less faithfully, the potential changes occurring at the adjacent epicardial surface. Those esophageal curves of Case 1 and those precordial curves of Case 2 in which the exploring electrode was close to the infarcted region are similar in general outline. In both cases the RS-T segment is displaced downward and the T-deflection is sharply upright. In the case of the QRS deflection the resemblance is somewhat less striking, but both sets of curves display a con-

spicuous summit at the onset of the QRS interval, indicating initial negativity of the exploring electrodes. In other words, the initial downward movement present at the beginning of the QRS interval in normal precordial curves and in the curves obtained from the lesser levels of the esophagus in normal subjects is absent. The initial summit in question is much larger in the precordial curves (Case 2) than in the esophageal curves (Case 1); in the latter it is followed by a conspicuous downward movement. A similar summit occurs in the first three esophageal curves of our normal subject (Fig. 1), but not in the others from lower levels. No initial summit occurs in the esophageal curves at the ventricular level of Case 2, in the precordial curves of Case 1, or in the precordial curves of the normal subject.

In electrocardiographic studies of experimental infarcts produced in dogs by coronary ligation, Wilson and his associates¹⁷ have shown that the curves, obtained by leading directly from the surface of infarcts which are composed of dead muscle and extend completely through the ventricular wall, closely resemble those obtained by leading directly from the ventricular cavity beneath the infarcted region. In this case the dead muscle of the infarct appears to act as a window or opening in the ventricular wall, which permits the potential variations of the ventricular cavity to be transmitted to the epicardial surface. The valvular orifices at the base of the heart act in the same way, and leads from points in close proximity to and facing these orifices display a large initial upward or minus deflection at the beginning of the QRS group similar to that seen in leads from the ventricular cavity or from the surface of an infarct. This, no doubt, explains the occurrence of an initial summit in leads from the auricular levels of the esophagus in normal subjects (Fig. 1).

In direct leads from experimental infarcts which involve only the subendocardial layers of muscle the initial summit is smaller. It does not constitute the sole QRS deflection, as it does when the infarct extends completely through the ventricular wall, but is followed by a conspicuous downward movement which terminates in a sharp upward movement or intrinsic deflection of subnormal amplitude. The relatively small size of the initial summit and the deep downward movement following it in the esophageal curves of Case 1 (Fig. 2) suggest that the infarct did not involve the entire thickness of the ventricular wall. The anterior infarct of Case 2, on the other hand, did apparently penetrate the ventricular wall if we may judge by the form of the corresponding precordial leads, in which a large initial summit is the sole deflection of the QRS group.

In animal experiments¹⁹ pronounced RS-T displacement in the downward or plus direction occurs in direct leads from the surface of the infarct for a few hours immediately following coronary ligation. It disappears when the injured muscle dies or recovers. Wilson and his associates²⁰ have shown in experiments on the turtle heart

that in direct leads from the side of the heart opposite the injured region the RS-T displacement is in the upward or negative direction. It will be noted that in Case 1 the leads from the lower levels of the esophagus show conspicuous downward displacement of the RS-T segment, whereas in the precordial leads and in the first esophageal lead (at 37.5 cm.) the RS-T displacement is in the upward direction. The presence of marked RS-T displacement in this case suggests that the infarction is still in an early stage and that much of the damaged muscle is still alive. The small size of the initial QRS summit of the esophageal leads may be due in part to this cause.

In direct leads from experimental infarcted animal hearts striking T-wave changes of the type seen in human coronary occlusion are compared to leads from the marginal portion of the infarct.^{17, 18} These T-wave changes appear to depend upon a disturbance in damaged but not fatally injured muscle, which alters the retreat of the exciting process. When the exploring electrode is not in contact with the epicardial surface but merely close to it, the curve obtained represents the average of the potential variation occurring over a considerable area. It may be for this reason that precordial leads and esophageal leads frequently yield curves which combine features seen in direct leads from the central portion of an experimental infarct with features peculiar to direct leads from the marginal portion. In other words, fully developed QRS changes and fully developed T-wave changes may be present together in precordial (Fig. 3) or in esophageal leads.

CASE PROTOCOLS

CASE 1.—E. E., a white male, aged fifty-nine, entered the Boston City Hospital on Dec. 15, 1936 and died forty-eight hours later. He had suffered from malaria when in the Philippine Islands in 1900 to 1901 and had been treated with quinine for seven years. Though high blood pressure had been discovered five years previous to admission, he had been well until the day before, when he had short attacks of substernal pain which radiated to the left arm and were accompanied by a feeling of constriction around the chest, difficulty in breathing, and sweating. Two of these attacks occurred during the day while he was working and the third awakened him during the night. Each attack lasted for about two to five minutes. While walking to work on the day of admission he again suffered from the same symptoms, which were slightly but very temporarily relieved by nitroglycerine. The pain and constriction in the chest became very severe and he vomited and felt faint. An injection of morphine after admission to the hospital was necessary to provide relief.

Examination revealed a slightly cyanosed man who (after morphine) was not uncomfortable. The cardiac apex was found to be in the fifth intercostal space 1 cm. outside the midclavicular line. The cardiac rhythm was regular and the rate 90. The heart sounds were indistinct, but no murmurs or pericardial friction were heard. The blood pressure was 140/96. There was no cervical venous distension and no hepatic enlargement, though a few coarse rales were heard in both lungs. There was no peripheral edema. The temperature on admission was 97.6° F.

Laboratory Data.—The urine contained a small trace of albumin. The hemoglobin and red blood cell count were normal. The leucocytes were increased to 21,250 per

cubic millimeter on the day of admission but fell to 7,200 on the third day. Blood nonprotein nitrogen was 29 mg. per cent. The Hinton test on the blood was negative for syphilis. The corrected sedimentation rate was 34 mm. (Wintrobe method) in one hour on December 15, and 13 mm. on December 17.

Course.—The temperature rose to 100° F. on the second day and to 100.2° on the third day. Throughout the second day and until the early afternoon on the third day he felt perfectly comfortable. The esophageal electrode was swallowed on the second day without discomfort or any untoward sign. At 2:00 P.M. on the third day, while he was consulting his lawyer, he suddenly became acutely dyspneic and cyanosed and died within five minutes. Permission for autopsy was refused. No digitalis was administered throughout the course of the illness.

CASE 2.—B. C., a white male, aged forty-nine, entered the Boston City Hospital on Jan. 15, 1937, and was discharged on March 6, 1937. One month before admission he first suffered from short attacks of dull squeezing pain in the chest, brought on by exercise and relieved by rest. These became more frequent ten days before admission. On the morning of the day of admission he was attempting to rise from bed when he was seized by a very severe constricting pain in the chest which became worse, caused nausea and vomiting and necessitated two injections of morphine before he was brought to hospital.

Examination revealed an acutely ill man complaining of precordial pain. The cardiac apex was found to be in the fifth intercostal space, 10 to 11 cm. to the left of the midsternal line. The cardiac rhythm was regular and the rate 100. The heart sounds were faint but no murmurs, gallop rhythm, or pericardial friction were heard. The blood pressure was 140/90. Cervical venous distension, peripheral edema, and hepatic enlargement were absent, but a few moist râles were heard at the left lung base. The temperature on admission was 97° F.

Laboratory Data.—The urine contained a small trace of albumin; hemoglobin and red cell count were normal. The leucocytes were increased to 11,500 per cubic millimeter, but returned to normal on the third day. The blood nonprotein nitrogen was 30 mg. per cent. The corrected sedimentation rate (Ernstene method) was 0.3 mm. per minute. The Hinton test on the blood was negative for syphilis. X-ray cardiac measurements, made two weeks after admission, were as follows: To the left of the median line 11.5 cm., to the right 6 cm., internal diameter of the thorax 33.5 cm. and great blood vessels 8 cm.

Course.—The temperature rose on the second day and remained at 101° F. for three days. The pulse rate fell gradually to about 80. On the fourth day a pericardial friction rub was heard at the right sternal border in the fourth intercostal space which disappeared on the following day. The blood pressure fell to 94/50 on the tenth day, and on discharge was 100/60. Some precordial discomfort remained for three weeks but thereafter the convalescence was uneventful. The esophageal electrode was swallowed on February 23 without discomfort or any untoward sign. No digitalis was administered throughout the course of the illness.

SUMMARY

1. Standard leads, unipolar extremity leads, unipolar precordial leads, and unipolar esophageal leads were employed in a normal subject, in a case of infarction of the posterior wall of the heart and in a case of infarction of the anterior wall of the heart.

2. These curves have been analyzed and compared and it has been found that the precordial electrocardiograms characteristic of anterior infarction resemble the esophageal electrocardiograms characteristic of posterior infarction, and vice versa.

3. In general the curves here presented provide evidence that the potential variations occurring at the epicardial surface of myocardial infarcts in man are similar to those which occur at the epicardial surface of infarcts produced in animals by coronary ligation.

We are deeply indebted to Dr. Frank N. Wilson for his very helpful criticism.

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COMPARATIVE EFFECTS OF WATER BATHS AND MUSTARD BATHS AT VARYING TEMPERATURES ON THE RATE OF PERIPHERAL BLOOD FLOW IN MAN

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THE ever increasing number of reports in medical literature of clinical and experimental studies of the peripheral vascular system in man point to a growing interest among both clinicians and experimentalists in variations in rates of peripheral blood flow in both physiologic and pathologic states. This interest has been stimulated largely by the development of simplified and practicable apparatus for recording skin surface temperatures and for photographing the capillaries of the skin at the nail fold; excellent modifications of these methods have been developed by Wright and Duryee.¹ Application of these procedures to the clinical study of the peripheral vascular system in several peripheral circulatory clinics has revealed frequent and marked depression of the skin surface temperature and stoppage of blood flow in the capillaries of the extremities in a variety of pathologic states and in apparently normal subjects in response to drugs and some foods and after smoking tobacco.^{2, 3, 4} Although results obtained by these procedures should be accepted as qualitative indications only, not as quantitative measurements, they emphasize both the frequency of depressions in peripheral blood flow and the need of a simple and readily available method for prevention of, and relief from, disturbances of the peripheral blood circulation.

Wright and Duryee,⁵ in their excellent review of the present knowledge concerning human capillaries, point out that the capillary bed is responsive to chemical influences by local reactions, usually by dilatation (only in special or pathologic cases by general reactions) and to nervous stimulation, usually by constriction, over the body as a whole. It is, therefore, likely that beyond the arterioles the capillaries and venules function actively, thereby participating directly in vascular reactions. Although it has long been known that mustard baths improve the peripheral circulation, Mattill⁶ in his review of the literature on hydrotherapy cites only one reference to mustard baths in which it had been shown that the addition of mustard to a bath at neutral temperatures increased the oxygen consumption and the carbon dioxide output by 25 per cent although the bath alone had no demonstrable influence on metabolism.

The experiments herein reported were undertaken to determine quantitatively the effects of adding mustard to water baths at temperatures between 25° C. and 40° C. upon the rate of peripheral blood flow in the hand or foot immersed in the bath. With this objective in mind, com-

parisons have been made of the effects of mustard baths and water baths at similar temperatures. Lampson⁷ applied Freeman's modification of the method of Hewlett and van Zwaluwenberg⁸ to a quantitative study of the vasoconstriction induced by smoking. This procedure was adopted in the experiments described below. In order to observe changes in rates of blood flow in the foot, a plethysmograph, which accommodates the foot comfortably, was constructed. Fig. 1 gives the sketch of this apparatus and the method of insertion of the foot and of supporting the leg.

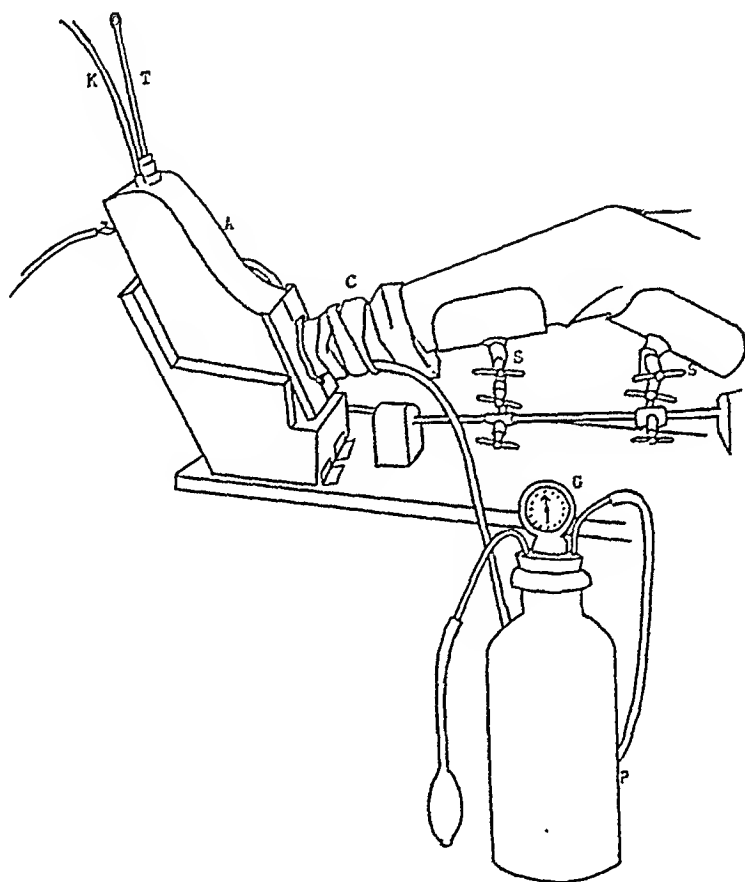


Fig. 1.—A, the brass plethysmograph into which the foot has been inserted.
T, thermometer inserted into the bath with the plethysmograph.
K, rigid rubber tubing leading from the plethysmograph to the Brodie bellows.

C, cuff to shut off return of venous blood from foot.
P, pressure bottle.
G, pressure gauge.
SS, supports for leg.

Three normal men and six normal women, whose ages varied from 21 to 32 years, served as experimental subjects.

In all experiments the room temperature was maintained between 18° and 20° C. Before the tests, the subjects were given periods of complete rest varying from thirty to sixty minutes. During the experimental period the subjects reclined at rest on a couch provided with a comfortable back rest. Either the right arm or the right foreleg was supported on a horizontal plane above the level of the heart.

Hewlett and van Zwaluwenberg have stated that in favorable cases the error of the method does not exceed 20 per cent. In the experience of the authors, the probable experimental error of the method is ± 15 per cent with the hand plethysmograph and ± 12 per cent with the foot plethysmograph. These have been estimated from the mean average deviations in the rate of peripheral blood flow during control periods in all experiments, of which the average results have been summarized in Table I.

TABLE I

VARIATIONS IN RATES OF PERIPHERAL BLOOD FLOW IN EXTREMITIES OF EXPERIMENTAL SUBJECTS DETERMINED AT DIFFERENT TIMES

SUBJECT	NUMBER OF DETERMINATIONS	LENGTH OF EXPERIMENTAL PERIOD IN MINUTES	EXTREMITY USED	PERIPHERAL BLOOD FLOW AS INCREASE IN VOL. OF EXTREMITY C.C. MIN.			AVERAGE RATE OF INFLOW OF BLOOD PER 100 C.C. HAND OR FOOT PER MINUTE
				MAXIMUM	MINIMUM	AVERAGE	
R.B.	6	35	hand	39	35	36.3	6.7
	4	17	hand	26	22	24.6	4.5
	3	25	hand	25	23	24.4	4.5
L.L.	3	15	hand	10	8	8.8	3.2
	5	30	hand	7	5	5.3	1.9
	5	30	hand	13	8	11.6	3.3
D.L.	6	30	hand	11	8	9.3	2.3
	4	16	hand	6	5	5.6	1.4
	6	15	hand	19	11	14.0	3.5
M.L.H.	6	25	hand	34	29	32.4	7.8
K. B.	4	30	hand	9	8	8.4	2.4
A.S.	5	52	hand	13	8	9.6	3.0
	6	55	hand	28	20	24.0	7.5
C.K.	7	46	hand	20	10	17.5	3.7
	4	26	hand	20	8	12.6	2.6
	5	27	hand	37	27	31.8	6.1
N.K.	9	41	foot	23	17	21.1	3.1
	9	26	foot	18	12	14.5	2.0
L.L.	9	32	foot	22	12	17.3	2.6
	10	50	foot	34	23	27.9	4.2
C.K.	4	31	foot	20	10	14.0	1.3
	3	24	foot	17	11	13.2	1.1
	6	45	foot	17	12	15.6	1.4
	6	40	foot	32	17	28.2	2.5

Table I presents data for rates of peripheral blood flow either in the hands or the feet of the experimental subjects determined during control periods on different days but under similar experimental conditions. Variations from 50 to 150 per cent have been found in the results obtained at different times for any one subject. Hewlett and van Zwaluwenberg have reported equally variable results for the same individual at different times. Since only well-trained subjects were employed in these experiments and they remained at rest during the experimental periods and since the temperature within the plethysmograph was main-

tained within $\pm 1^{\circ}$ C. and variables in the environment were excluded, it seems that the factors producing the variations noted are probably beyond the control of the experimenter. In order to exclude variations in peripheral blood flow when determined on different days, the effects of

TABLE II

COMPARATIVE EFFECTS OF BATHS IN WATER AND IN MUSTARD WATER UPON THE RATE OF PERIPHERAL BLOOD FLOW

SUBJECT	EXTREMITY	BATH	AVERAGE TEMPERATURE OF BATH $^{\circ}$ C.	EXPERIMENTAL PERIOD MINUTES	NUMBER OF DETERMINATIONS	RATE OF PERIPHERAL BLOOD FLOW AS INCREASE IN VOLUME OF EXTREMITY—C.C. PER MINUTE		
						MAXIMUM	MINIMUM	AVERAGE
L.L.	hand	Water	37.0	15	3	10	8	8.8
		0.5 per cent mustard	37.0	45	7	22	14	18.0
D.L.	hand	Water	35.0	16	4	6	5	5.6
		0.6 per cent mustard	35.0	46	8	11	5	8.3
C.K.	hand	Water	34.9	30	6	58	29	40.5
		0.6 per cent mustard	35.1	34	4	68	56	61.2
L.L.	foot	Water	36.6	50	10	31	23	27.9
		0.6 per cent mustard	36.8	55	9	47	36	41.5
L.L.	foot	Water	35.9	32	9	22	12	17.3
		0.6 per cent mustard	36.1	46	7	48	33	42.7
N.K.	foot	Water	35.0	41	9	23	17	21.1
		Water	40.5	33	6	50	40	44.9
		0.6 per cent mustard	40.8	31	6	57	46	50.9
N.K.	foot	Water	35.5	26	9	18	12	14.5
		Water	38.2	49	9	42	21	30.7
		0.6 per cent mustard	38.1	66	9	50	38	42.2
C.K.	foot	Water	34.9	49	5	93	29	38.4
		0.6 per cent mustard	35.0	60	4	65	43	50.6
C.K.	foot	Water	39.8	33	5	82	61	68.2
		0.6 per cent mustard	39.8	36	5	114	92	100.6
J.D.	foot	Water	39.9	31	5	108	82	99.6
		0.6 per cent mustard	39.9	31	7	152	128	139.7

mustard baths have been determined by comparing the rates of blood flow into the hand or foot, immersed in mustard baths, with rates found on the same day during control periods immediately preceding the mustard baths. During the control periods the hands or feet of the subjects were immersed in water maintained at a temperature similar to that of the mustard bath.

In Table II are reported results of three experiments made on hands and seven experiments on feet showing the comparative effects of water and mustard baths upon the rate of blood flow in these extremities at temperatures between 35° C. and 40° C. In the preparation of the mustard baths, enough mustard was weighed out to give a final concentration of 0.6 per cent mustard. This was stirred well into a small volume of water for about two minutes and was then added to the total volume of water to be used in the bath. In all experiments the same volume of the hand or foot was inserted into the plethysmograph in the water bath as in the mustard bath periods. At the end of the water bath period the water was withdrawn from the plethysmograph and replaced by the mustard solution. Results are presented in Table II for rates of blood flow, as increases in volumes of the hand or foot, calculated in cubic centimeters per minute, for the total volume of the hand or foot inserted into the plethysmograph. Throughout the periods during which determinations of rates of blood flow were made, the temperatures of the fluids within the plethysmograph were maintained constant within $\pm 0.4^{\circ}$ C.

In all experiments, immersion of the hand or foot in a mustard bath produced an increase in the rate of flow of blood into these extremities above the levels found for the water baths under like experimental con-

TABLE III

COMPARATIVE EFFECTS OF WATER BATHS AND MUSTARD BATHS AT VARYING TEMPERATURES UPON THE PERIPHERAL BLOOD FLOW IN EITHER THE HAND OR THE FOOT

SUBJECT AND PART IMMERSED IN BATH	BATH	AVERAGE TEMPERATURE °C.	TIME IN MINUTES	NUMBER OF DETERMINATIONS	AVERAGE RATE OF BLOOD FLOW C.C. PER MINUTE PER 100 C.C. EXTREMITY	
C. K. Hand	Water	25.0	44	5	2.0	± 0.36
		30.1	46	7	3.7	± 0.65
		34.9	29	6	8.6	± 1.93
		39.7	39	4	15.5	± 0.62
		44.8	27	4	17.1	± 1.15
	Controls in water	25.0	17	3	2.2	± 0.66
		29.9	26	4	2.6	± 0.80
	0.6 per cent mustard	25.2	32	4	1.9	± 0.35
		30.2	34	4	9.3	± 0.97
		35.1	34	4	12.6	± 0.67
		40.0	23	4	14.5	± 1.97
C. K. Foot	Water	25.3	31	4	0.9	± 0.07
		30.2	40	4	1.3	± 0.27
		34.9	49	5	3.5	± 0.42
		39.8	34	5	7.9	± 0.98
		44.8	22	5	14.8	± 0.58
	Controls in water	25.0	16	3	0.9	± 0.13
		29.9	24	3	1.1	± 0.16
	0.6 per cent mustard	25.1	25	4	0.9	± 0.15
		30.3	34	4	1.6	± 0.17
		35.0	26	4	4.1	± 0.57
		40.0	25	4	13.2	± 0.80

ditions. The average rates of blood flow into the hand, when immersed in mustard, were from 48 to 125 per cent (average 74 per cent) greater than when immersed in water. In the seven experiments on the foot, the rates of blood flow were from 11 to 146 per cent (average 51 per cent) greater with mustard baths than with water baths.

Comparative effects of exposing the surface of the skin to temperatures below and above the average skin surface temperature upon the

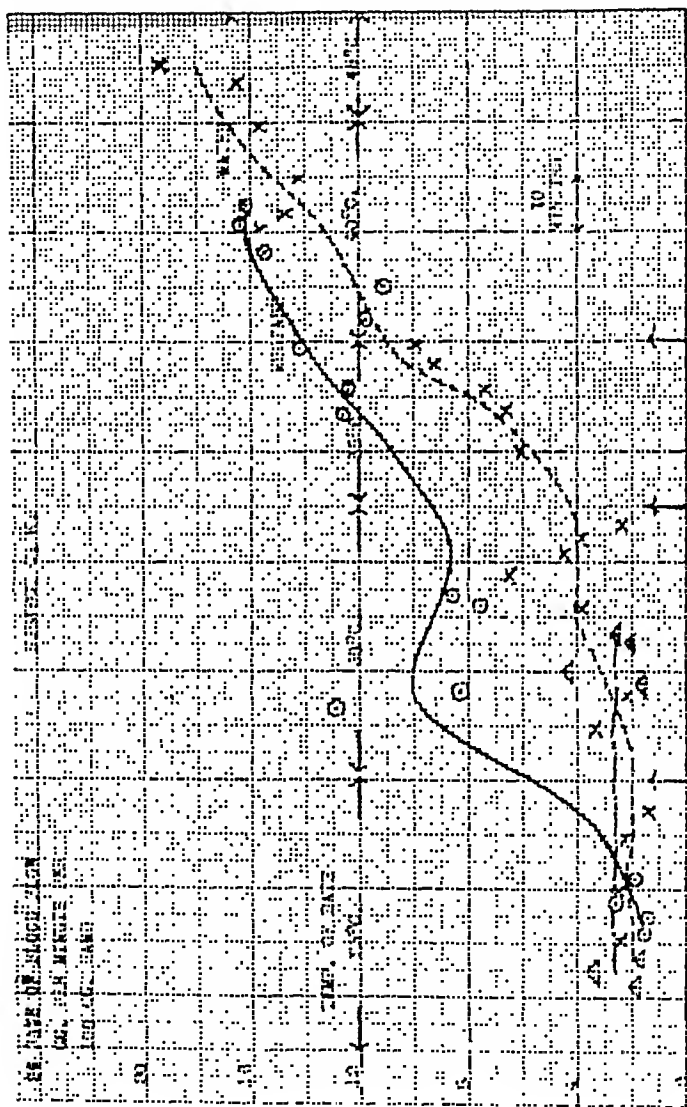


Fig. 2.—Comparative effects of water baths and mustard baths at varying temperatures upon the rate of peripheral blood flow in the hand.

rate of blood flow in the hand and in the foot have been observed in two series of experiments of which the results are reported in Table III. Temperatures of the baths in the plethysmographs between 33 and 35° C. were found to approximate closely the subjects' estimates of their skin temperatures. When the temperatures of the baths were maintained within this range, the subjects noted no differences between the temperature of the bath and the temperature of their skins.

Determinations of rates of blood flow were begun only after the extremity had been adjusted to the temperature after immersion for from 10 to 15 minutes. The comparative experiments with water and with mustard baths were carried out on different days. However, on the days of the experiments with mustard, control periods preceded the use of the mustard baths. In these control periods, either the hand or the foot was immersed in water at 25° C. and 30° C. Results obtained during

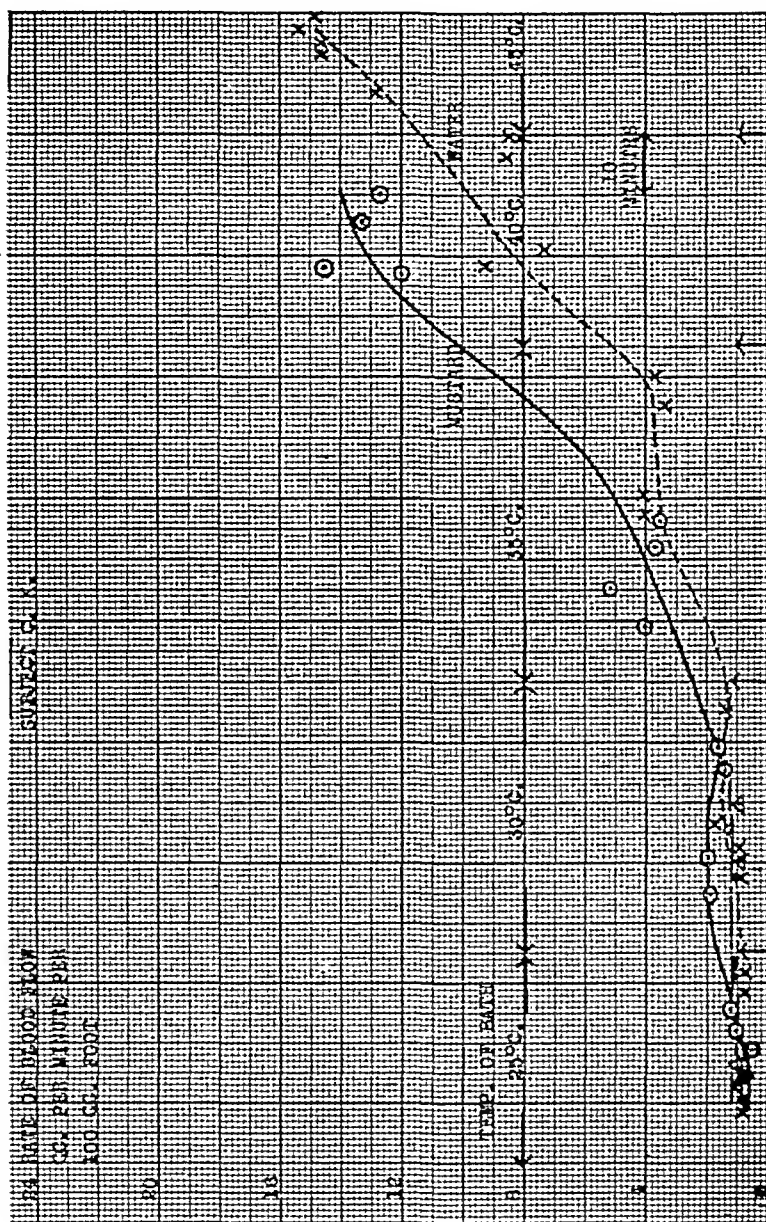


Fig. 3.—Comparative effects of water baths and mustard baths at varying temperatures upon the rate of peripheral blood flow in the foot.

these control periods confirm the findings for the water baths at these temperatures noted on the days of the water bath experiments.

Cooling the surface of the skin of the hand by immersing it in water at 30° C. decreased the average rate of blood flow to 43 per cent, and cooling it in water at 25° C., to 23 per cent of the average level at 35° C. Elevating the temperature of the water bath to 40° C. increases the rate of flow of blood into the hand by 80 per cent. At a temperature of 25° C. there was noted no significant difference between the effects of

the water bath and the effects of the mustard bath upon the rate of peripheral blood flow into the hand, but at 30° C. the average rate of blood flow into the foot is 3.5 times the average rate in the mustard bath as compared with the water bath at 30° C. on the same day, and 2.5 times that of the day of the water bath experiments. At 35° C. the difference between the effects of the mustard bath and the water bath were less marked. At this temperature the average rate of blood flow in the hand immersed in the mustard bath is 46 per cent greater than the average rate in the water bath. At 40° C. the difference between the average rates for the mustard bath and the water bath are within the limits of experimental error of the method. Fig. 2 summarizes these data as curves showing changes in rates of blood flow in the hand immersed either in a water bath or in a mustard bath at temperatures varying from 25° C. to 40° C. for the mustard bath and from 25° C. to 45° C. for the water bath.

Similar responses in the peripheral blood flow to changes in the temperature of the baths were noted in experiments on the foot. Cooling the surface of the skin of the foot by immersing the foot in baths at 25° C. depresses the rate of blood flow into the foot to 25 per cent of the average rate for the water bath at 35° C. At 30° C. and 35° C. in these experiments, the mustard bath did not significantly increase the rate of blood flow above the average levels for the water bath. However, when the foot was immersed in the mustard bath at 40° C., the average rate of peripheral blood flow into the foot was 67 per cent greater than the average rate for the water bath at the same temperature.

Results of these comparative experiments with water baths and mustard baths on the foot are presented in the curves of Figure 3. Significant differences between the effects of the water bath and mustard bath appear only at a temperature of 40° C. In the mustard bath at this temperature, the rates of flow of blood into the foot are approximately equivalent to the rates determined in the water bath at 45° C.

SUMMARY

1. Mustard baths* containing 0.6 per cent mustard have accelerated the rate of peripheral blood flow into both hands and feet above the levels found for water baths at similar temperatures, between approximately 35° C. and 40° C. In three experiments on the hand the average increase found for the mustard baths above the levels of the water baths was 74 per cent. In seven experiments on the foot, the average increase found for the mustard baths above the levels for the water baths was 51 per cent.

2. Cooling the surface of the skin of either the hands or the feet, by immersion in water at 30 to 25° C., depresses the rates of peripheral

*The authors wish to take this opportunity of thanking the manufacturers of Colman's mustard for supplying the dry mustard used in these experiments.

blood flow to levels of 40 to 25 per cent of the average levels at the average normal temperature of the skin.

3. In comparative experiments at 25° C. on one subject there was noted no significant difference between the effects of mustard baths and water baths upon the rates of peripheral blood flow in the hands. However, adding mustard to the water at 30° C. markedly increased (150 per cent) the rate of peripheral blood flow in the hand above the level for the water bath. At 35° C. a smaller difference was noted (46 per cent), and at 40° C. no significant difference was found between the effects.

4. At temperatures of 25 and 30° C. the mustard bath did not affect the rate of peripheral blood flow in the foot more than the water bath. At temperatures between 35 and 40° C., the mustard bath did increase the rate of blood flow from 17 to 69 per cent above the average rates for water baths at these temperatures.

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THE ELECTROCARDIOGRAPHIC CHANGES FOUND IN 22 CASES OF CARBON MONOXIDE (ILLUMINATING GAS) POISONING*

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IN A PREVIOUS investigation Shillito, Drinker, and Shaughnessy⁴ (1936) described certain neurologic sequelae in carbon monoxide poisoning. The other great field upon which attention has been focused in this condition is that of the cardiovascular system. There have been a number of electrocardiographic studies on experimentally asphyxiated animals, but only in a single instance have the electrocardiographic findings in poisoned patients been reported. Therefore, it seemed worth while to study a series of such cases by means of the electrocardiograph. The twenty-two cases upon which this paper is based are typical of those admitted to a city hospital.

All of the patients were admitted directly to the emergency ward upon their arrival at the hospital. However, before being removed from the scene of their asphyxiation, they had been treated with 7 per cent carbon dioxide and 93 per cent oxygen inhalations for varying lengths of time. Thus, when these patients were first seen by the clinicians, they were no longer in a state of asphyxiation, large experience having demonstrated that only innocuous amounts of carbon monoxide remain in the blood after the routine inhalation treatment given either by the gas company or police emergency squad. The physiologic abnormalities which may be present in such patients upon admission to the hospital, and thereafter, should be regarded as the sequelae of anoxemia rather than as symptoms of residual anoxemia. We had hoped to be able to obtain some electrocardiograms upon profoundly asphyxiated patients (i.e., before they had received any carbon dioxide and oxygen inhalations), but because of practical difficulties this attempt had to be abandoned. Therefore the electrocardiograms in this series represent the cardiac status following, rather than during, the period of anoxemia.

Table I summarizes the relevant facts concerning these cases. It should be understood that in calculating the duration of unconsciousness, no attempt has been made to estimate how long the patients were unconscious preceding discovery. Also, the time is conservative from

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the standpoint of recovery of consciousness, as many patients later had no recollection of experiences occurring at a time when they had been regarded as conscious.

In Table II are listed the changes found in each electrocardiogram, the time after admission at which it was taken, and the patient's blood pressure at that time. Only positive findings are recorded.

It was possible to locate only seven of the surviving twenty patients for a follow-up after they had left the hospital. The electrocardiographic findings thus obtained are incorporated in Table II.

Inasmuch as the clinical course of this group of cases was rather stereotyped, we are presenting brief histories of only three typical cases.

CASE 3.—The patient was a fifty-four-year-old white male who was found unconscious in a gas-filled room. He received inhalations for forty minutes and was said to have been conscious at the end of the treatment. On admission he was confused and disoriented, and appeared markedly dehydrated. Later the history was obtained that he had been on a four-day drinking bout.

The admission temperature was 101.8° F., pulse 110, blood pressure 130 systolic, 90 diastolic. The lungs were clear except for occasional wheezes. The heart was not enlarged. The sounds were of poor quality and the rhythm was regular. There were no signs of cardiac failure. Peripheral arteries were moderately thickened.

An electrocardiogram taken two and one-half hours after admission showed a regular rhythm, with a rate of 100 per minute. Noteworthy changes were rather low P-waves in all leads, a flat T-wave in Lead I and an upright T-wave in Lead IV.*

For the first two days after admission the patient was confused and drowsy but was mentally clear thereafter. During this time and for several more days he ran a low-grade fever, the result of a mild bronchitis. An electrocardiogram taken on the second hospital day showed more normal P-waves. The T-waves were as on the preceding day. An electrocardiogram on the third day again showed rather low P-waves, as on the first day. A fourth electrocardiogram, taken on the tenth day, showed flat P-waves in Lead II, inverted P-waves in Lead III. In the first lead T-waves were inverted, and in the second lead were very low with a slight late rise. T₁ was again upright.

The patient went home on the fourteenth day, free from complaints. It was impossible to locate him later for further study.

CASE 7.—The patient was a sixty-five-year-old white male chronic alcoholic. When found, approximately one hour before admission to the hospital, he was lying completely unconscious in a gas-filled room with one unlighted stove burner blowing gas. The breathing was reported as slow and gasping, the lips blue, and the body cold. Artificial respiration was applied for eight minutes before the arrival of the Emergency Squad, at which time 7 per cent oxygen and 93 per cent carbon dioxide inhalations were started. After thirty minutes the condition of the patient was improved sufficiently for him to be removed by ambulance to the hospital, inhalations being continued there for fifteen minutes.

On admission the patient was somewhat irrational. The temperature was 96° F., the pulse 124, and the blood pressure 120 systolic and 80 diastolic. There were a few bronchial wheezes throughout the chest. The heart was not enlarged. The

*Lead IV, the chest lead, was taken in all the cases of the present series with exploring electrode at the cardiac apex, indifferent electrode on the left leg, and polarity so arranged that electrical negativity is represented by upward deflections and positivity by downward deflections.

TABLE

CASE NO.	DATE OF ADMIS- SION	AGE	SEX	ALCO- HOL.	CONDITION WHEN FOUND	ARTIFICIAL RESP.	CO ₂ -O ₂ INHALA- TION	CONDITION ON ADMISSION
1	1/17/37	30	M	Yes	Unconscious	20 min.	1 hr. 15 min.	Semicomatose, re- sponding to pain
2	1/18/37	23	M	No	Unconscious	None	1 hr. 8 min.	Comatose
3	1/25/37	54?	M	Yes	Unconscious	None	40 min.	Confused and disori- ented
4	1/26/37	65?	M	Yes	Unconscious	None	2 hr.	Comatose
5	2/ 2/37	38	M	Yes	Unconscious	None	1 hr. 15 min.	Comatose
6	2/17/37	45	M	No	Unconscious	10 min.	40 min.	Stuporous
7	2/21/27	65	M	Yes	Unconscious	8 min.	47 min.	Irrational
8	2/21/37	68	M	Yes	Unconscious	8 min.	47 min.	Irrational
9	2/26/37	75	M	No	Unconscious	None	38 min.	Semicomatose
10	2/27/37	70	M	No	Unconscious	12 min.	43 min.	Stuporous
11	3/ 1/37	52	M	No	Unconscious	None	1 hr. 5 min.	Semicomatose
12	3/ 3/37	59	M	Yes	Unconscious	6 min.	1 hr. 18 min.	Semicomatose
13	3/ 3/37	82	M	No	Semiconscious	None	30 min.	Conscious negativis- tic
14	3/ 8/37	73	M	No	Unconscious	None	33 min.	Conscious
15	3/21/37	79	F	No	Unconscious	25 min.	40 min.	Stuporous
16	3/30/37	72	M	Yes	Unconscious	20 min.	66 min.	Stuporous
17	3/30/37	40	M	No	Unconscious	None	35 min.	Dull and drowsy
18	3/31/37	40	M	Yes	Unconscious	24 min.	2 hr. 27 min.	Comatose
19	4/ 9/37	56	F	No	Unconscious	10 min.	18 min.	Disoriented
20	4/10/37	54	M	Yes	Unconscious	None	45 min.	Drowsy and con- fused
21	4/21/37	57	M	No	Unconscious	10 min.	1 hr.	Drowsy
22	4/22/37	25	M	No	Unconscious	None	40 min.	Stuporous

PROBABLE DURATION OF UNCONSCIOUS- NESS	ON ADMISSION			HEART EXAMINATION	DEGREE OF ARTERIO- SCLEROSIS	RESULT
	TEMP. (° F.)	PULSE	BLOOD PRESSURE			
2 hr.	98.0	100	130/80	Normal.	0	Home on 3rd day.
12+ hr.	102.8	136	140/90	Normal.	0	Home after 7 days.
40 min.	101.8	110	130/90	Normal in size. Sounds distant.	++	Home on 14th day.
45 hr. (Died with- out regaining conscious- ness)	97.0	90	110/60	Normal in size. Sounds distant and of poor quality.	+++	Died on 3rd day.
3 hr.	98.6	132	90/65	Normal	0	Home on 4th day.
1+ hr.	94.6	96	150/90	Normal in size. Auricular fibrillation. Sounds of poor quality. No murmurs.	+	Home after 2 wk. in custody of brother. (Incompetent to take care of himself.)
1+ hr.	96.0	124	120/80	Normal in size. Sounds of fair quality. S ₂ hollow. Short systolic blow at apex.	++	Home on 2nd day.
1+ hr.	95.4	116	105/60	Normal in size. Sounds distant. No murmurs.	+++	Home on 2nd day.
1+ hr.	98.2	128	100/60	Normal in size. Sounds of fair quality. No murmurs.	+++	Home on 2nd day.
3+ hr.	95.0	128	160/95	Normal in size. Sounds of poor quality. No murmurs.	+++	Died suddenly on 6th day.
5 hr.	96.4	120	110/70	Normal.	0	Home on 2nd day.
1½ hr.	96.0	110	108/76	Normal in size. Sounds of fair quality. Localized systolic blow at apex.	++	Home on 8th day.
30 min. (Semicon- scious)	98.4	108	120/80	Sounds of poor quality. No murmurs.	++++	Home on 3rd day.
40 min.	95.4	120	132/66	Sounds loud and ringing. Systolic blow at apex. Size? (emphysema)	++++	Home on 2nd day.
1 hr.	96.6	76	170/64	Sounds loud, of poor quality. Short, rough systolic murmur at apex.	+++	Home on 4th day.
1½ hr.	97.0	86	110/50	Normal in size. Sounds loud. Systolic blow at apex.	+++	Observation in psychopathic division.
50 min.	97.8	128	130/100	Normal.	0	Home on 5th day.
11 hr.	95.0	114	100/60	Normal in size. Sounds of fair quality. No murmurs.	+	Home on 3rd day.
40 min.	95.0	116	140/70	Enlarged to left, 15 cm. in sixth intercostal space. Sounds of fair quality. No murmurs.	+++	Home on 2nd day.
45 min.	96.0	120	90/60	Normal.	+	Home on 3rd day.
2 hr.	98.0	58	128/80	Normal.	+++	Home on same day.
1 hr.	97.6	114	88/65	Normal.	0	Home on 8th day.
15 min.						

TABLE II

CASE NO.	DATE	TIME AFTER AD-MISSION	BLOOD PRES-SURE	RATE	RHYTHM	P-WAVES	PR	QRS	S-T	T-WAVE
1	1/17/37	15 min.	130/80	116	Regular	Normal	Normal	Normal	Rather level S-T ₄	Late dip in Leads I, II, and III. Notch at end of T ₄ .
	1/18/37	29 hr.	124/70	66	Regular	Normal	Normal	Normal		
2	1/18/37	5 min.	140/90	130	Regular	Normal	Normal	Widened S in Leads I, II, and III. S-wave less wide.	S-T ₄ convex, elevated, and high. S-T ₄ high in origin but no longer upright.	T ₁ slightly diphasic. Low origin of T ₂ and T ₃ . T ₁ now upright.
	1/18/37	7 hr.	135/80	120	Regular	Normal	Normal			
	1/19/37	27 hr.	110/75	About 90	Sinus arrhythmia	Normal	Normal	S-waves still a little prominent in Leads II and III.		Fairly normal in all leads.
	1/20/37	52 hr.	110/70	70	Sinus arrhythmia	Normal	Normal	Same	Same	Same
	1/23/37	5 days	114/70	72	Regular	Normal	Normal	S ₂ and S ₃ within limits of normal variation.	Normal	Essentially normal.
3	1/25/37	2 hr. 35 min.	130/90	100	Regular	Rather low in all leads	Normal	S ₁ is down, as well as Q and R.	Normal	T ₁ flat, T ₄ upright.
	1/26/37	18 hr.	130/86	95	Regular	More normal	Normal	Normal	Normal	Unchanged
	1/27/37	44 hr.	140/90	74	Regular	As on first day	Normal	Normal	Normal	T ₁ low, slightly upright, T ₄ shallow.
	2/ 4/37	10 days	130/80	66	Regular	P ₂ flat, P ₃ inverted	Normal	Normal	Normal	T ₁ inverted, T ₂ very low with late slight rise, T ₄ upright.

TABLE II—Cont'd

4	1/26/37	30 min.	110/60	88	VPC, left	Normal	Normal	Tendency to low voltage. Lead I = +5 Lead II = +4 Lead III = -1	Normal	T ₁ rather low, T ₂ shallow.
	1/27/37	27 hr.	134/70	130	Regular	Normal	Normal	Same	Normal	Same
5	2/ 2/37	20 min.	90/65	130	Regular	Normal	Normal	Normal	Normal	T ₁ low (0.5 mm.).
	2/ 3/37	29 hr.	130/80	89	Regular	Normal	Normal	Normal	Normal	T ₁ slightly higher (1 mm.).
6	2/17/37	5 hr.	150/90	AR 340 VR 90	A.F. (course)	-----	-----	S wide in all leads.	Normal	T ₁ upright, T ₂ low, T ₃ inverted.
	2/18/37	26 hr.	145/90	VR 78-88	A.F. (less coarse)	-----	-----	S, upright	Normal	Same
	2/19/37	52 hr.	145/80	AR 390 VR 80	A.F.	-----	-----	Same	Normal	T ₂ and T ₃ shallower.
	2/20/37	3 days	140/84	VR 80	A.F.	-----	-----	Same	Normal	T ₁ deeper again.
	2/23/37	6 days	138/80	VR 64	A.F.	-----	-----	Same	Normal	T ₁ flat.
	3/ 1/37	12 days	140/80	VR 50	A.F.	-----	-----	Same	Normal	T ₁ very shallow.
7	2/21/37	15 min.	120/80	VR 155	A.F.	-----	-----	Normal	Depressed in Leads I, II, and III.	T ₁ upright.
	3/25/37	32 days	160/85	75	Regular	Normal	Normal	Normal	S-T ₁ elevated.	Normal
8	2/21/37	35 min.	105/60	VR 125	A.F.	-----	-----	Tendency to low voltage. Lead I = +2, -5 Lead II = +4, -1 Lead III = +1 to 2, -1 to 2	S-T ₁ upcurved with high origin. S-T ₂ slightly sagging.	T ₁ low.
	3/25/37	32 days	150/75	75	Regular	Normal	Normal	Voltage normal	Normal	T ₁ shallow.
9	2/26/37	20 min.	100/60	130	APC	-----	-----	Normal	S-T ₁ somewhat convex	T ₁ rather low.
	2/26/37	14 hr.	110/65	110	Regular	Normal	Normal	Normal	Normal	Normal
	5/ 3/37	66 days	160/90	94	Regular	Normal	Normal	Normal	Normal	T ₂ inverted.

TABLE II—Cont'd

CASE NO.	DATE	TIME AFTER AD- MISSION	BLOOD PRES- SURE	RATE	RYTHM	P-WAVES	PR	QRS	S-T	T-WAVE
10	2/27/37	20 min.	160/95	130	Regular	P ₂ and P ₃ rather high	Normal	Tendency to- wards low volt- age	Normal	T ₂ high, T ₁ low.
	2/28/37	24 hr.	120/85	134	Regular	Same	Normal	Same	Normal	T ₁ flat, T ₄ shallow.
	3/ 1/37	52 hr.	145/90	100	Regular	Lower	Normal	Little change	Normal	T ₁ low, but slightly higher than on preceding tracing; T ₄ more shallow; T ₂ low.
11	3/ 1/37	45 min.	110/70	115	Regular	Normal	Normal	Normal	Normal	T ₁ slightly low.
	5/11/37	74 days	145/90	78	Regular	Normal	Normal	Normal	Normal	Normal
12	3/ 3/37	35 min.	108/76	VR 130	A.F.	-----	-----	Normal	Normal	T ₁ very low.
	3/ 4/37	29 hr.	140/90	100	Regular	Normal	0.2 sec.	Voltage lower	Normal	
	3/ 5/37	51 hr.	110/75	70	Regular	Normal	0.16 sec.	QRS ₂ higher	Normal	T ₁ normal.
	3/10/37	7 days	120/65	78	Regular	Normal	0.16 to 0.18 sec.	Same	Normal	Normal
13	3/ 3/37	15 min.	120/80	122	Regular	Normal	Normal	Widened and notched in all leads, low volt- age.	Depressed in Leads I and II.	Diphasic T ₁ and T ₂ .
	3/ 4/37	26 hr.	130/84	85	Regular	Normal	Normal	Same except for higher voltage.	Same	Same
14	3/ 8/37	20 min.	132/66	130	A.F.	Normal	-----	Low voltage. Leads I, II, and III.	S-T ₁ and S-T ₂ sagging. S-T ₄ convex, with high origin.	Very low
	4/19/37	42 days	180/90	70	Regular	Normal	Normal	Improved volt- age.	Normal	Normal
								Lead I = +7		
								Lead II = +3, -2		
								Lead III = -5		

TABLE II—CONT'D

15	3/21/37	15 min.	170/64	72	Disturbance of auricular rhythm with variation in site of pace-maker.	Occasionally blocked. Sometimes inverted, or isoelectric.	Varies from 0.2 to 0.45 sec.	Slurred in Leads II and III.	Very low origin of S-T ₄ .	T ₂ and T ₃ inverted.
	3/22/37	24 hr.	174/70	65 to 70	Variation in site of pace-maker continuous.	Changes less marked than on preceding day.	Same	Same	S-T ₁ slightly depressed. Low origin of S-T ₄ continues.	T ₂ and T ₃ inverted.
	3/24/37	3 days	175/75	65 to 75	Disturbance of auricular rhythm decreasing.	Fairly uniform in shape. Occasional blocked p-waves.	As long as 0.4 sec. at times.	Same	Changes less marked.	T ₁ slightly upright. T ₂ and T ₃ inverted. Slightly low origin of T ₄ .
16	3/30/37	35 min.	110/50	About 90	Many VPC.	Normal	Normal	Normal	Normal	Low in Leads I, II, and III.
	3/30/37	7 hr.	110/60	100	Regular	Normal	Normal	Normal	Normal	T ₁ upright. Higher in all leads.
	4/ 3/37	4 days	135/70	82	Regular	Normal	Normal	Normal	Normal	Same
	5/ 8/37	39 days	165/90	78	Regular with rare VPC.	Normal	Normal	Normal	Normal	Same
17	3/30/37	1 hr. 15 min.	130/100	135	Regular	Normal	Normal	Slightly low voltage.	Normal	Normal
								Lead I = +4 Lead II = +3, -2 Lead III = +2, -6		
	3/31/37	23 hr.	120/95	95	Regular	Normal	Normal	Normal voltage	Normal	Slight late inversion of T ₁ ; T ₂ very low; T ₃ very shallow.
	4/ 3/37	4 days	125/85	104	Regular	Normal	Normal	Same	Normal	Low upright T ₁ ; T ₂ higher; T ₃ slightly inverted; T ₄ shallow.

TABLE II—CONT'D

CASE NO.	DATE	TIME AFTER AD-MISSION	BLOOD PRES-SURE	RATE	RHYTHM	P-WAVES	PR	QRS	S-T	T-WAVE
18	3/31/37	1 hr.	100/60	120	Regular	Normal	Normal	Normal	S-T ₁ rather level. S-T ₁ more normal.	T ₁ low. T ₁ low; slight dip at end of T ₂ and T ₃ ; late rise in T ₄ .
19	4/ 9/37	15 min.	140/70	104	Regular	Normal	0.19 sec.	Marked L.A.D.	Normal	T ₁ diphasic; T ₄ up-right.
	5/29/37	50 days	180/88	75	Regular	Normal	Normal	Same	Normal	T ₁ diphasic; T ₂ and T ₃ inverted; T ₄ diphasic.
20	4/10/37	1 hr.	90/60	105	Regular	Normal	Normal	Normal	Normal	T ₁ and T ₂ low.
	4/10/37	5 hr.	130/90	102	Regular	Normal	Normal	Normal	Normal	T ₁ and T ₂ higher.
	4/11/37	28 hr.	130/85	74	Regular	Normal	Normal	Normal	Normal	Normal
21	4/21/37	45 min.	120/80	55	Regular	Normal	Normal	Normal	Normal	Normal
22	4/22/37	25 min.	88/65	110	Regular	Normal	Normal	Normal	Normal	T ₁ low; T ₁ slightly shallow.
	4/23/37	24 hr.	100/70	64	Sinus arrhythmia	Normal	Normal	Normal	Normal	T ₁ very low; T ₄ slightly shallow.
	4/24/37	48 hr.	105/70	58	Sinus arrhythmia	Normal	Normal	Normal	Normal	T ₁ low; T ₄ more shallow.
	4/27/37	5 days	100/65	55	Sinus arrhythmia	Normal	0.19 sec.	Normal	Normal	T ₁ slightly higher; T ₄ shallow.
	4/29/37	7 days	106/70	50	Sinus arrhythmia	Normal	Normal	Normal	Normal	Normal

heart sounds were of poor quality. The rate was rapid and apparently regular. The liver was not enlarged; there were no râles at the lung bases and no peripheral edema. The peripheral vessels were moderately sclerotic.

An electrocardiogram was taken thirty minutes after the patient was admitted and showed auricular fibrillation with a heart rate of 155 per minute, depressed S-T segments in Leads I, II, and III, and an elevated S-T segment in Lead IV. The T-wave in Lead IV was upright.

Within three hours after admission the patient became less noisy and talked coherently. He left the hospital against advice early the next morning.

This patient was followed up one month later. At that time he denied noticing any ill effects from the gas poisoning. On examination his chest was clear, and the heart sounds were of better quality. His blood pressure was 160 systolic, 85 diastolic. An electrocardiogram taken at this time was essentially normal, the rhythm being regular at 75 per minute and the changes in the S-T segments and T-waves noted in the previous electrocardiogram being absent.

CASE 4.—This patient, an elderly white male, was found unconscious in his room which was filled with gas escaping from a leaking fixture. After being treated with carbon dioxide and oxygen inhalations for two hours he was brought to the hospital, still unconscious.

On admission the patient was in profound coma, with deep stertorous respiration, slight cyanosis of the lips, and cold extremities. The temperature was 97° F., the pulse 96, and the blood pressure 110 systolic and 60 diastolic. The lungs were clear except for a few wheezes. On percussion the heart was apparently normal in size. The sounds were distant and regular except for occasional extrasystoles. The liver was not enlarged, and there was no edema. Peripheral arteries were very sclerotic. Tendon reflexes were hyperactive, but there were no abnormal responses.

An electrocardiogram taken thirty minutes after admission showed ventricular premature contractions (left), with right axis deviation. The rate was 88 per minute. The QRS complexes showed a tendency to low voltage. T-wave changes were rather low T₁ and shallow T₂.

The next day the patient was still in coma. The temperature was 103.8° F., the respiration 48, and the blood pressure 134 systolic and 70 diastolic. Heart sounds were louder than on admission but of poor quality. There were many moist râles at both lung bases. The liver was not enlarged, and there was no edema. The white blood count at this time was 21,000, with 91 per cent polymorphonuclear leucocytes.

A second electrocardiogram was taken twenty-seven hours after admission. The rhythm had become regular, but the rate had increased to 130 per minute. The QRS complexes were of low voltage, as in the first electrocardiogram. No new changes had appeared.

The patient's temperature continued to rise and the moist râles at the lung bases increased. He died forty-two hours after admission without regaining consciousness. No autopsy was performed.

RESULTS

In our series of twenty-two cases of carbon monoxide asphyxia, the most common electrocardiographic deviation is an abnormality in the T-waves or in the level of the S-T segment, there being 18 such cases (Cases 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 20, and 22). Four cases (Cases 7, 8, 12, and 14) showed paroxysmal auricular fibrillation, and one (Case 2) showed transitory intraventricular block. Two (Cases 4 and 16) showed ventricular premature contractions, and one

(Case 9) auricular premature contractions. Low voltage on the initial electrocardiogram, later improving or returning to normal, was present in five cases (Cases 4, 8, 13, 14, and 17). Variations in the P-waves occurred in two (Cases 3 and 10).

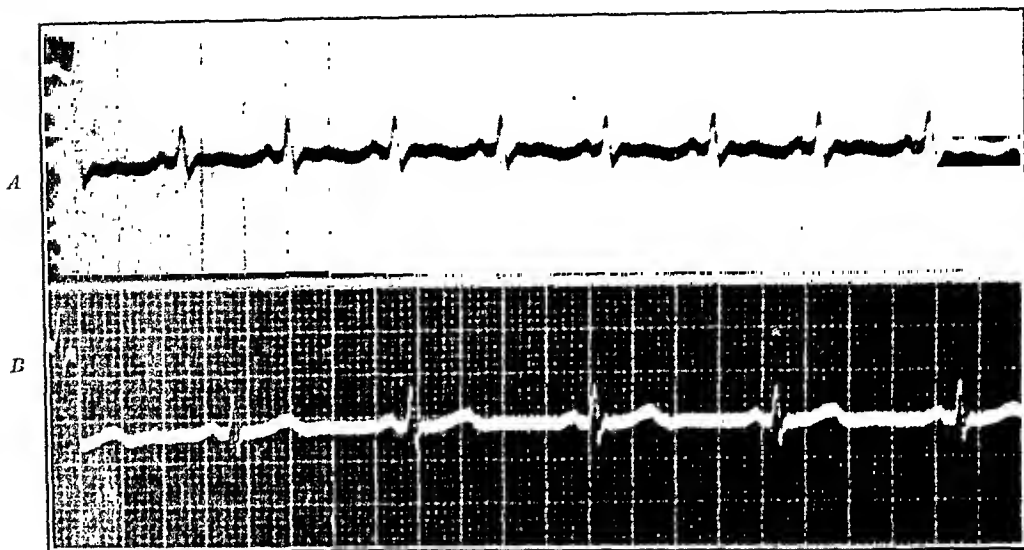


Fig. 1.—A, Lead I from Case 2 on admission to the hospital, showing low diphasic T-waves. B, Lead I from Case 2, five days later, normal.

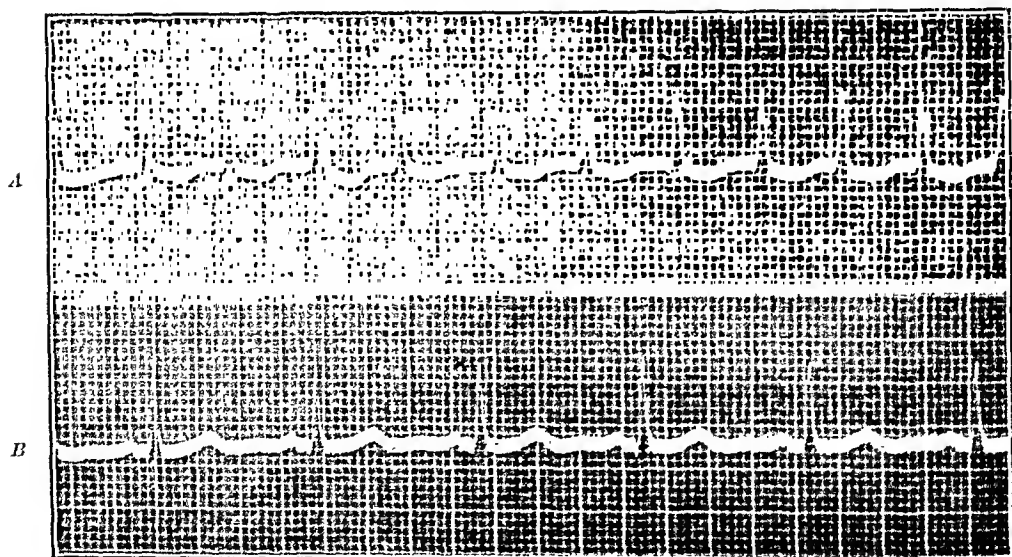


Fig. 2.—A, Lead I from Case 7 on admission to the hospital, showing auricular fibrillation and depressed T-waves. B, Lead I from Case 7, thirty-two days later, normal.

We feel that the above changes, having been transitory, may be ascribed directly to the carbon monoxide asphyxia, except when coronary disease may have paved the way in some cases. However, the importance that can be attached to the poisoning in several other cases is less clear-cut. In Case 15 there was a marked disturbance of auricular rhythm,

with variation in the site of the pacemaker. This had decreased three days after admission when the last electrocardiogram was taken and when the patient was lost for further study, but, lacking a follow-up, the most that can be said is that the asphyxia probably aggravated a condition already present in a seventy-nine-year-old woman who had arteriosclerosis and hypertension.

In regard to Case 6, doubt again exists as to the rôle played by the asphyxiation. This forty-five-year-old man gave no history of any symptoms suggestive of preexisting heart disease, and examination yielded no clue as to an etiology for such disease. Yet, upon his admission to the hospital, auricular fibrillation was found to be present. Electrocardiograms taken through the twelfth day of his two-week stay in the hospital all showed auricular fibrillation and intraventricular block. The evidence is far from conclusive that the changes found in this patient were solely the result of his carbon monoxide poisoning. It is more probable that he had preexisting auricular fibrillation and intraventricular block on a basis of coronary disease.

In Case 13 no definite conclusions can be drawn as to the etiology of the intraventricular block which was present, this patient being 82 years of age, markedly arteriosclerotic, and providing no follow-up after the second day. It is quite possible that coronary disease and gas poisoning each played a rôle.

DISCUSSION

We have found one report of a patient overcome by carbon monoxide who was followed with frequent electrocardiograms (Colvin,¹ 1927). A young man seriously poisoned by gasoline exhaust was completely comatose on admission to the hospital and was given inhalation treatment. Approximately seven hours after admission the patient could be roused, but he was mentally dull for three days. An electrocardiogram taken twenty-four hours after the poisoning occurred showed intraventricular block; a second electrocardiogram taken three days after the poisoning showed improvement but still indicated impaired conduction in the ventricles. By the sixteenth day all abnormal changes had disappeared, and the patient was considered perfectly sound.

As noted already our findings are limited to the period of recovery from the marked anoxemia after emergency oxygen and carbon dioxide treatment. How much more extensive and uniform the electrocardiographic changes might have been at the height of the poisoning, we have no knowledge; it seems likely that they would have been greater than at the stage of our examination. So far as they go, our results, while indicating that intraventricular block may result from carbon monoxide poisoning, suggest that such is not the usual finding. Case 2 is the only one which can be said to show this type of conduction disturbance as an aftermath of asphyxia. Furthermore, this patient, who was uncon-

scious for over twelve hours, showed only the merest trace of intraventricular block twenty-seven hours after admission. Five days after admission his electrocardiogram was essentially normal. Whether or not the fact that the patient reported by Colvin was overcome by gasoline exhaust, whereas our patient was overcome by illuminating gas, accounts for the much more prolonged conduction disturbance in the former case is problematical.

In general our results tend to agree with those obtained by Haggard² (1921) in his work with dogs. Gassing dogs to death rapidly (twenty-five to forty minutes) with a high concentration of gas, and more slowly (five to seven hours), using lower concentration of carbon monoxide, and taking electrocardiograms at intervals, he found that "no evidence of impairment of cardiac conduction developed until respiration had failed." When an extreme degree of asphyxia was present, the most characteristic change was heart-block. As pointed out earlier, none of our patients was seen at the stage of such profound asphyxia. However, Haggard gassed three dogs to the stage at which artificial respiration was necessary to bring about their recovery. Electrocardiograms for the first four hours showed tachycardia with T-waves in the direction opposite to normal. Electrocardiograms taken after twenty-four hours showed normal rate and T-waves. Similarly, two out of three animals gassed into the stage of complete respiratory failure, with the development of partial heart-block as shown by electrocardiogram, were revived with 8 to 10 per cent carbon dioxide in oxygen inhalations. A few minutes after the cessation of the inhalation treatment all evidence of impaired conduction had disappeared. Although the preceding experiments were carried out using a mixture of pure carbon monoxide and air, Haggard found that the results were essentially the same when an illuminating gas and air mixture was used.

The changes in the T-waves and in the S-T segments which some of our cases demonstrated are somewhat similar to those reported by Katz, Hamburger, and Schutz³ (1934) in experimentally produced generalized anoxemia. Their subjects rebreathed air from which the carbon dioxide was removed, and electrocardiograms were taken at stages of extreme oxygen deprivation. The "most consistent changes in the electrocardiogram were a flattening of the T-wave in one or more leads, in some instances followed by its inversion. . . . In practically every instance, the level of the S-T segment tended to be shifted downward during anoxemia," the maximum effect being observed when the oxygen content was lowest, and the changes tending to disappear rapidly upon resumption of breathing room air.

CONCLUSIONS

1. Carbon monoxide asphyxia, even though severe enough to cause death, may produce no important electrocardiographic changes.

2. Changes in the T-waves and in the S-T segments occur most frequently.

3. Paroxysmal auricular fibrillation may occur, as a rule in patients within the age group in which any physiologic insult or trauma may cause this condition.

4. One case of transitory intraventricular block is present in the series.

5. No cases of auriculoventricular block definitely attributable to carbon monoxide poisoning were found, although one case is reported in which a marked disturbance of auricular rhythm with partial auriculoventricular block was apparently aggravated by the asphyxia.

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THE BLOOD PRESSURE AND THE SIZE OF A CARDIAC INFARCT*

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DURING the course of studies on the action of certain drugs in cardiac infarction in the cat,^{1, 2} there occurred an opportunity to make observations on the level of the systemic blood pressure three weeks after ligation of a coronary artery and on the relation of the blood pressure to the size of an infarct, the area of which was accurately measured. So far as we know, this subject has received little attention in survival experiments after production of a cardiac infarct. Several of the more important studies are listed.³

The blood pressure was determined in 27 cats three weeks after ligation of a large coronary artery (the left circumflex at its origin in all instances but one); in 12 control animals three weeks after the main branches of the left coronary artery had been similarly exposed but not ligated; and as further control, in a group of nine normal (unoperated upon) animals. At this time, when examined by the "blind test," the control animals were as a rule indistinguishable from those in which infarction was present. Mean blood pressure was recorded by a mercury manometer, by means of a cannula inserted in the carotid artery under local anesthesia. Several readings were taken when the animal was quiet, and the average of these was calculated. This average will be referred to as the mean blood pressure.

Approximately one-half the animals with infarction were treated with aminophylline during the three weeks after operation, but, since the behavior of the blood pressure in this group was essentially the same as in that not treated with this drug, all the animals with infarction are presented in this study as a single group. Details of the treatment by aminophylline, the operative techniques, and the measurement of the infarct by means of the planimeter have been described,¹ and the blood pressure figures in the individual experiments are included in another report.²

The results are summarized in Table I. The average mean blood pressure was essentially the same for all groups of animals: after cardiac infarction 150 mm., after the control operation 155 mm., and in the unoperated controls 152 mm., the average for all controls being 154 mm. The range in mean blood pressure for the individual experiments was also similar in the control (120 to 185 mm.), and in the infarcted (120

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to 183 mm.) groups. Under the conditions of these experiments, therefore, the level of the blood pressure was normal three weeks after acute infarction.

The data were analyzed to ascertain whether an animal with a large infarct was more likely to have a low blood pressure than one with a small infarct. Plotting mean blood pressure against infarct size failed to reveal a correlation between these two variables (Fig. 1). Furthermore, it was found (Table I) that when the animals having the small-

TABLE I
ANALYSIS OF THE BLOOD PRESSURE IN RELATION TO INFARCT SIZE

GROUP	NUMBER OF ANIMALS	MEAN BLOOD PRESSURE MM. HG	SIZE OF INFARCT SQ. CM.	DIFFERENCE ABOVE OR BELOW MEAN PRESSURE OF CONTROLS PER CENT
Control Animals	21	154	none	0.0
Infarcted Animals	27	150	5.55	-2.6
<i>Infarcted Animals</i>				
Smallest infarcts	13	153	3.60	-0.6
Largest infarcts	14	147	7.36	-4.5
Smallest infarcts	5	151	2.92	-1.3
Largest infarcts	5	144	9.29	-6.5
Highest mean pressures	13	162	5.10	+5.2
Lowest mean pressures	14	139	5.96	-9.7
Highest mean pressures	5	172	4.51	+11.7
Lowest mean pressures	5	129	6.61	-16.2
<i>Control Animals</i>				
Highest mean pressures	10	167	none	+8.5
Lowest mean pressures	11	141	none	-8.5
Highest mean pressures	5	176	none	+14.3
Lowest mean pressures	5	133	none	-13.6

est infarcts and those having the largest infarcts were grouped separately, the average mean pressure did not deviate more than 6.5 per cent from the normal in either case, although the average infarct size in one group was more than three times as large as that in another. When those groups having the highest and lowest pressures were examined separately, it was found that those having the lowest pressures also had on the average somewhat the larger infarct. That this might be purely accidental, however, was suggested by the finding that these low pressures were not appreciably lower than those among a similar small number of normal animals, similarly selected.

That the blood pressure was normal three weeks after coronary occlusion and that this was so in the case of both very large and very small infarcts were unexpected results. They are in contrast to those which prevail in clinical coronary thrombosis, as in a high proportion of these cases the blood pressure does not return to its previous level.⁴ The reasons for these differences between the cat and the human are not

clear, but, in attempting to explain them, consideration should be given to possible differences in the reflex compensatory mechanisms for maintaining blood pressure in the two species, to differences in the location of the infarct, for the artery most frequently occluded in man is the anterior descending branch of the left coronary rather than the left circumflex,^{4, 5} and to the fact that in the cat, except for the infarct, the heart and blood vessels are normal, whereas in man infarction is usually associated with additional pathologic changes in the cardiovascular system. It is conceivable that the nature or extent of these latter changes may be partially disclosed by the behavior of the blood pressure after infarction, and some light, therefore, may be thrown on prognosis. Levine and Brown⁴ state that in coronary thrombosis it is their "general impression that the patients who have done the best were those who

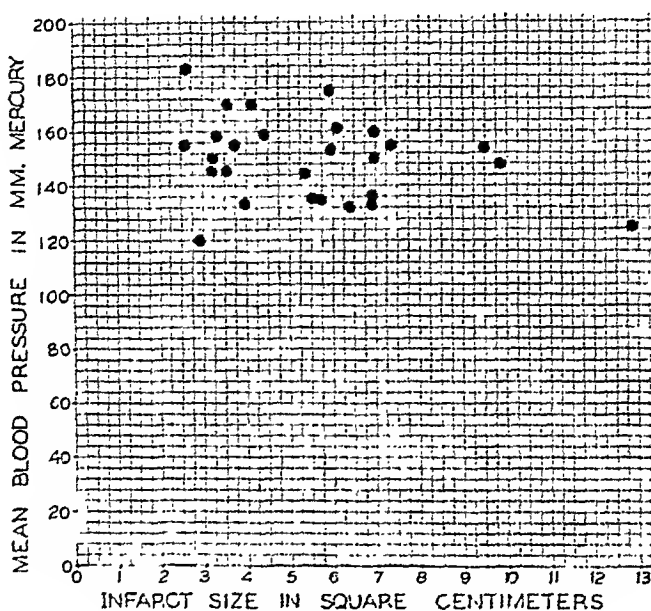


Fig. 1.—Mean blood pressure is plotted against infarct size. Note the wide scatter of the points, and lack of correlation between the two.

showed a marked fall with only a slight increase in the blood pressure." The majority of clinical surveys on the course and prognosis of this disease,⁶ except in regard to its association with hypertension, pay scant attention to the significance of changes in the systemic blood pressure subsequent to the acute attack. We have not determined the complete course of the blood pressure changes after infarction, inasmuch as the operation for experimental coronary occlusion introduces serious technical difficulties. Our results, as far as they go, however, indicate that the fairly rapid restoration of the normal blood pressure is likely to prove misleading if used as a basis for an inference regarding the size of the infarct. They should serve to focus attention on the need for systematic correlations between the blood pressure curve, post-mortem findings and prognosis in clinical coronary thrombosis.

SUMMARY

In the cat with an otherwise normal circulation, the blood pressure is almost invariably normal three weeks after the ligation of a large coronary artery (left circumflex). This applies to infarcts of widely different sizes, ranging from a relatively small area involving the upper third of the left ventricle posteriorly to a very large one including nearly all of the left ventricle posteriorly, together with adjacent strips of the right ventricle and interventricular septum.

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THE CORONARY VASOCONSTRICTOR ACTION OF FOREIGN SPECIES BLOOD*†

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DURING the course of preliminary studies in developing a method for perfusion of the coronary arteries in the beating heart of the dog, tests were run using freshly defibrinated blood of the sheep, beef, and pig (obtained from the slaughter house through the courtesy of Dr. D. Klein, of Wilson Laboratories) as a perfusate. It was soon apparent that this foreign species blood was incompatible with the isolated beating heart when employed in the same manner as dog blood (Katz, Jochim, and Bohning¹), and, after a number of attempts to make this foreign blood suitable, its use was discontinued. Evidence was obtained in the course of these experiments that the incompatibility of the foreign species blood for our purpose was due largely to the persistence of a coronary vasoconstrictor action. We consider this coronary vasoconstriction by foreign blood of sufficient importance to merit the presentation of our findings.

EXPERIMENTAL DATA

We first tested the effect of the foreign species blood on the blood pressure when injected repeatedly into normal dogs anesthetized with nembutal. During each injection, an equal amount of the dog's own blood was removed to keep the blood volume constant.

For the first experiment the defibrinated beef blood was filtered six times through a fine meshed cloth in preparation for injection into the animal. The first substitution of 100 c.c. of beef blood caused a profound drop in mean blood pressure after a short lag, and it required about 15 minutes for the blood pressure to return to normal. After two such substitutions, a 50 c.c. substitution had practically no effect, but a 200 c.c. substitution, which was tried next, caused so profound and sustained a pressure drop that the animal died. On post-mortem examination marked pulmonary edema was found.

In the second dog the first substitution of 100 c.c. of blood also caused a delayed, profound and prolonged depressor effect, but this was preceded by a definite pressor effect. This was the only experiment in the course of this work in which such a preliminary pressor action was noted. Repetition of this substitution, which was done twenty-nine times, resulted in a progressive diminution and ultimate

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†Aided by the Emil and Fanny Wedeles Fund for Cardiac Research.

abolition of the depressor response without any apparent effect on the preliminary pressor response. This animal was in good condition when killed one and one-half hours after the first beef blood substitution.

In the third dog, segments of whose blood pressure curve are shown in Fig. 1, the filtered beef blood was passed through the lungs of a dead dog to see if this would abolish the depressor effect. It was found that the first substitution still caused a delayed, profound, and prolonged depressor effect. Repetition of this substitution carried out twenty-five times led to the diminution and ultimate abolition of this depressor effect. The dog was in good condition when killed three and one-half hours after the start of the first substitution. A similar abolition of the depressor effect of beef blood was obtained in three other dogs.

These experiments indicated that the injection of slaughter house blood into the living animal causes a depressor action to which the

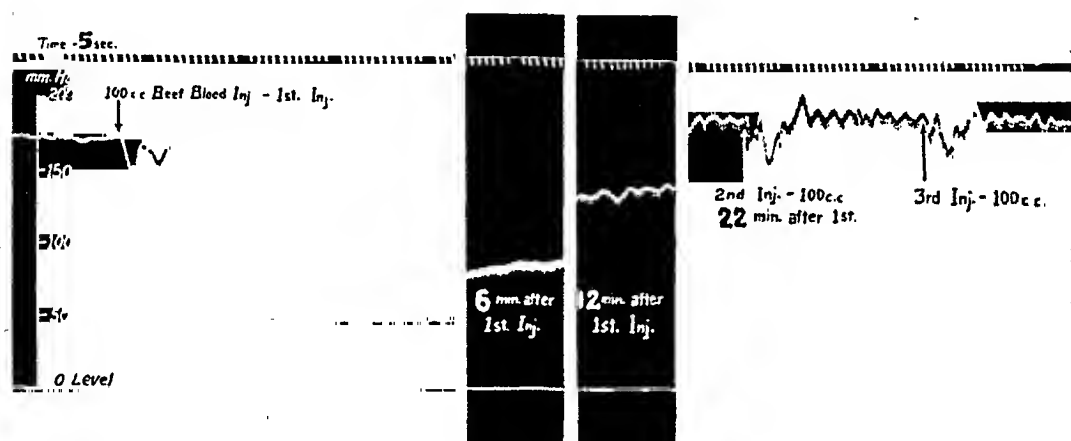


Fig. 1.—Blood pressure curve from an anesthetized dog to show the typical effect of repeated substitutions of 100 c.c. of beef blood for an equal amount of the dog's blood. The disappearance of the profound delayed depressor response seen in injections subsequent to the first is clearly visible. Discussed in text.

dog can be made refractory. Since similar depressor responses did not occur when we used hemoglobin solutions of beef blood, prepared according to the technique of Amberson and his co-workers,² the depressor response must have been due to a foreign element in the serum.

Following this experience, we made it a routine practice to make the recipient dog refractory to this depressor action before establishing the isolated beating heart preparation. In principle we followed the method employed in desensitizing patients susceptible to horse serum. Usually we began with an intravenous injection of 5 e.e. of a 1:5 dilution of beef blood in isotonic saline. Gradually increasing doses were given as the animal became more refractory until 5, 10, 50, and 100 c.c. of whole beef blood could be given without causing a depressor response. Our earlier experience showed that this refractory state lasted several hours—sufficient time in which to make and conduct experiments in the isolated heart preparation.

However, actual trial in the use of this foreign blood to perfuse the coronary circuit in the beating heart according to the technique employed previously with dog's blood¹ met with failure, even though the recipient dog had become refractory to the depressor action. Whenever used, the heart of the isolated preparation after developing premature systoles went into ventricular fibrillation, and this occurred at most within five minutes after the coronary arteries were cannulated, and often even before the cannulation was completed. In all instances except one, no measurable coronary flow could be obtained, although the coronary inflow pressure was anywhere between 100 and 150 mm. Hg. In the one instance, a flow of 60 c.c. per minute was obtained for a few minutes after the coronary cannulation was completed, but the flow soon stopped entirely. Autopsies showed that in these animals the coronary

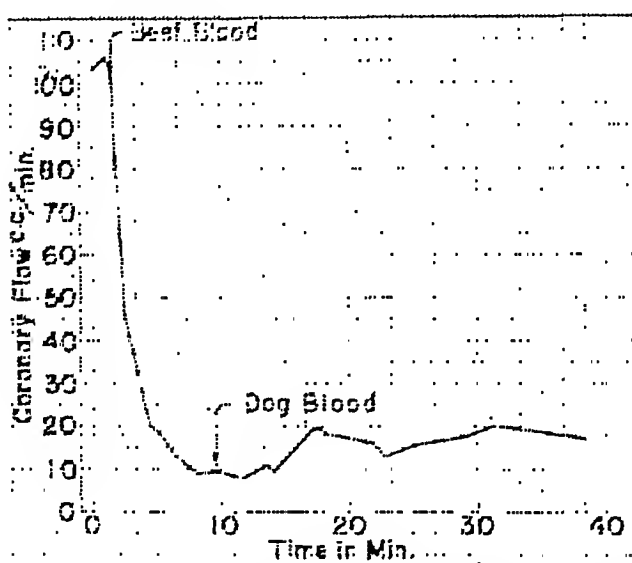


Fig. 2.—Coronary blood flow changes produced in an isolated fibrillating dog heart by substituting as a coronary perfusate beef blood, to the depressor action of which the dog had been made partially refractory. Discussed in text.

arterial and sinus cannulae were in place and not kinked and that the major superficial coronary arteries were patent.

This experience suggested that the deleterious action of beef blood on the isolated dog heart was due to a vasoconstrictor action of the beef blood on the coronary vessels. This conclusion was verified by actual test in an isolated fibrillating heart, the coronary vessels of which were perfused with beef blood after the dog had been made refractory to the depressor action of the beef blood. The preparation was first established with dog's blood as the perfusate in the manner previously described by us.³ After the coronary flow had become stabilized, the beef blood, prepared in exactly the same way as the dog's blood,² was substituted as a perfusate, and after a few minutes again replaced

²The dog's blood used as a perfusate was obtained from several dogs as previously described.¹

with dog's blood. The results on coronary flow are shown in Fig. 2. It will be seen that during the perfusion with beef blood a marked coronary vasoconstriction appeared, and the coronary flow decreased to 9 per cent of its previous level. This marked decrease in flow was only slightly relieved when the preparation was reperfused with dog's blood, the flow remaining at a level of 18 per cent of its original value. Histologic examinations of this heart by Dr. Otto Saphir, of the Department of Pathology, revealed no significant intravascular clotting. The absence of intravascular clotting and the tendency for the constriction to be reversed by dog's blood indicates that the serum of this foreign blood contains a vasopressor substance for the dog's coronary vessels.

The presence of this coronary vasopressor response in the perfused heart and its absence in the entire animal made refractory to the de-

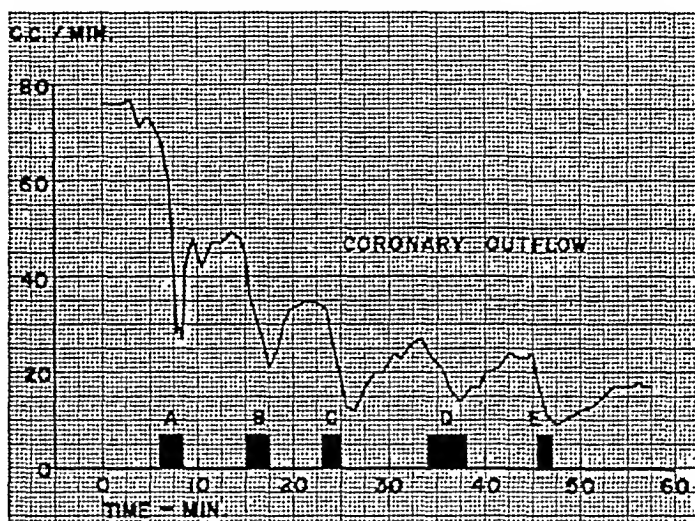


Fig. 3.—Coronary blood flow changes produced in an isolated fibrillating heart by the following bloods:

A, 100 c.c. of blood from a dog made refractory to the depressor action of beef blood (containing 10 per cent beef blood).

B, 120 c.c. of normal dog blood to which 5 per cent beef blood had been added.

C, 70 c.c. of the same blood as A except for the addition of 5 per cent more beef blood.

D, 95 c.c. of normal dog blood to which 20 per cent beef blood had been added.

E, 50 c.c. of whole beef blood. Discussed in text.

pressor action of beef blood might be due to (a) the greater concentration of beef blood reaching the heart in the former case, (b) the use of blood from dogs not made refractory to the depressor action of beef blood in the initial perfusion, or (c) the absence of a refractory state in the heart to the action of beef blood, the protection of the heart in the whole animal being the result of the action of other organs which are removed in making the isolated heart preparation. Two types of experiments were devised to test these possibilities. In the first, an isolated fibrillating heart preparation such as used in the preceding experiment³ was made in a dog which had previously been made refractory to the depressor action of the beef blood. The dog's

blood for the perfusate was obtained from animals not previously exposed to beef blood. At varying intervals small quantities of the following bloods were substituted as a perfusate: (a) blood from a dog made refractory to the depressor action of beef blood; this contained roughly 10 per cent beef blood accumulated in the process of rendering the animal refractory; (b) a 5 per cent solution of beef blood in the dog's blood used in the original perfusion; (c) a 5 per cent solution of beef blood in the dog's blood used in (a), really making a 15 per cent beef blood solution; (d) a 20 per cent solution of beef blood in the dog blood used in the original perfusion; and (e) whole beef blood. All the bloods used were defibrinated and prepared in the usual manner. The foreign blood could be temporarily substituted as a perfusate under the same pressure and temperature as the original blood used for perfusion simply by turning a stopcock when desired. The results of this experiment are shown in Fig. 3. It will be seen that all five samples containing beef blood caused a reversible vasoconstriction of the coronary vessels, the constriction tending to be abolished when the original dog's blood perfusate was again used. This experiment shows that the presence of blood derived from an animal made refractory to the depressor action of the beef blood did not appreciably modify the vasoconstrictor action of beef blood.

The second type of experiment was to note the effect of substituting whole beef blood for dog's blood as a perfusate in an isolated fibrillating heart preparation taken from a dog rendered so refractory to beef blood that the animal's entire blood volume could be rapidly changed without a depressor action. Two such experiments were carried out. In both, the animals were made so refractory to the depressor action of beef blood that 1100 c.c. and 1700 c.c. of beef blood, respectively, could be substituted for the animal's own blood in a matter of four and one-half and fourteen minutes without causing any appreciable blood pressure drop. In both these animals the isolated perfused fibrillating hearts were found to be refractory to the coronary vasoconstrictor action of beef blood when this was substituted as a perfusate for dog's blood. These last experiments indicate convincingly that the heart can be rendered refractory to beef blood provided the process is carried far enough. The apparent absence of refractoriness in the earlier experiments indicates merely that the process of rendering the animal refractory had not been carried far enough.

DISCUSSION

These results strongly suggest that the depressor action of the foreign blood in the dog may be contributed to by a cardiogenic factor resulting from the coronary vasoconstriction demonstrated in this isolated organ. It may prove to be that the serious and often fatal result obtained in

anaphylactic shock is in part contributed to by such a coronary vasoconstrictor action in susceptible individuals. This is in accord with the recent observations of Wilcox and Andrus,⁵ who demonstrated that coronary constriction occurred in an isolated guinea pig heart following the administration of the protein to which the animal had become sensitive. The evidence presented by Wilcox and Andrus that this coronary constriction is due to histamine is not in accord with observations made in this laboratory on the dog since we found that histamine causes coronary vasodilation.³

We have no evidence which could point to the nature of this coronary vasopressor substance; our previous results showing that acetylcholine is a coronary vasodilator³ would exclude this substance. We are reporting these experiences with beef blood since they show coronary vasoconstriction to a degree which may truly be called spasm. Apparently, the substance giving rise to this action is in the serum of the foreign blood and would appear to be of the nature either of a foreign protein or of one of its breakdown products.

The possibility that the foreign blood coronary "spasm" might be in the nature of a specific foreign protein affair raises the question as to whether or not similar types of reactions may not follow in susceptible individuals when foreign proteins enter the blood stream. We cannot resist the temptation to speculate that this may on occasion lead to severe coronary vasoconstriction in man and help to explain some cases of acute coronary insufficiency and angina pectoris, especially if the coronary vessels are already the seat of narrowing in the larger channels. Vasoconstriction affecting the smaller arteries under these circumstances would increase the resistance to flow in the already narrowed coronary bed. At present, however, this must be regarded as a mere conjecture. Our results lend support to the long-established clinical concept of intense coronary "spasm" since such a state had been demonstrated by our experiments to actually occur in the experimental animal.

SUMMARY

A delayed, profound, and prolonged depressor action occurred when a small amount of beef blood (also sheep's and pig's blood) was injected into a normal anesthetized dog. This depressor response could be progressively lessened and finally abolished by repeated injections of beef blood gradually increased in amount, the dog's own blood being withdrawn in equal amounts. When, however, this dog's heart was completely isolated and its coronary arteries were perfused with the same beef blood, ventricular fibrillation rapidly ensued, and the coronary inflow markedly decreased and finally stopped, indicating an intense coronary "spasm." Evidence is presented suggesting that

this is a real coronary vasoconstriction, and that the substance responsible for this is made ineffective in the whole animal and in the isolated heart when the animal is made sufficiently refractory to the depressor action by repeated passage of the beef blood through the animal.

We are indebted to the other members of the department for technical assistance.

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OCCLUSION OF THE CORONARY ARTERIES BY HEMORRHAGE INTO THEIR WALLS*

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OCCCLUSION of the coronary arteries may be the result of one of the following lesions or a combination of several of them: (1) thrombosis, (2) intramural coronary arterial hemorrhage, (3) severe arteriosclerosis with stenosis, (4) syphilitic aortitis and coronary arteritis with narrowing of the ostia, (5) endarteritis, and (6) embolism.

The commonest cause of occlusion is thrombosis of an artery which is the seat of severe partially occluding sclerosis. Intramural coronary arterial hemorrhage, which is probably the second most common cause, has received scant attention, and has never been considered as a cause of death. However, careful study shows that many coronary arteries are occluded not as the result of thrombosis but of massive hemorrhage into the vessel wall with the formation of a large hematoma which blocks the lumen either by virtue of its size or by rupture through the intima and subsequent development of a thrombus. The purpose of this report is to describe seven patients who died not as the result of thrombosis but of intrinsic intramural hemorrhage.

CASE REPORTS

CASE 5543.—A white man, 61 years of age, a restaurant proprietor, had noticed increasing dyspnea and fatigue upon exertion for ten months before admission to the hospital. He had been examined by a physician who sent him to bed and gave him digitalis. Nevertheless, his symptoms became worse, and he developed attacks of severe precardial pain which radiated down the left arm. The patient, as well as his mother and father, had diabetes mellitus.

The blood pressure was 140/80, the temperature 38° C., and the pulse 100. The heart was slightly enlarged, and the sounds were of poor quality, with a marked gallop rhythm and pulsus alternans. A soft blowing systolic murmur was heard over the aortic area and at the apex. There was marked cyanosis and dyspnea, with Cheyne-Stokes respiration. Congestive failure was severe. The white blood cell count was 8,600. The electrocardiogram showed notching of the QRS interval, with an abnormal S-T complex in Leads I and III. The P-R interval was 0.12 sec. This graph was interpreted as representing a combination of myocardial damage and digitalis effect. The patient's symptoms increased in severity, and he died four days after admission to the hospital and ten months after the onset of symptoms.

At autopsy the heart weighed 650 gm. There was both recent and remote infarction of the entire right ventricle, with mural thrombi in the right ventricle and auricle. The pericardial sac was obliterated by dense, fibrous adhesions.

*From the Institute of Pathology, Western Reserve University, and The University Hospitals.

Both coronary arteries showed severe sclerosis with narrowing of the lumen. The right coronary artery, at a point 5 cm. from the ostium, was occluded by soft, dark red blood clot. Serial sections through this portion showed intramural arterial

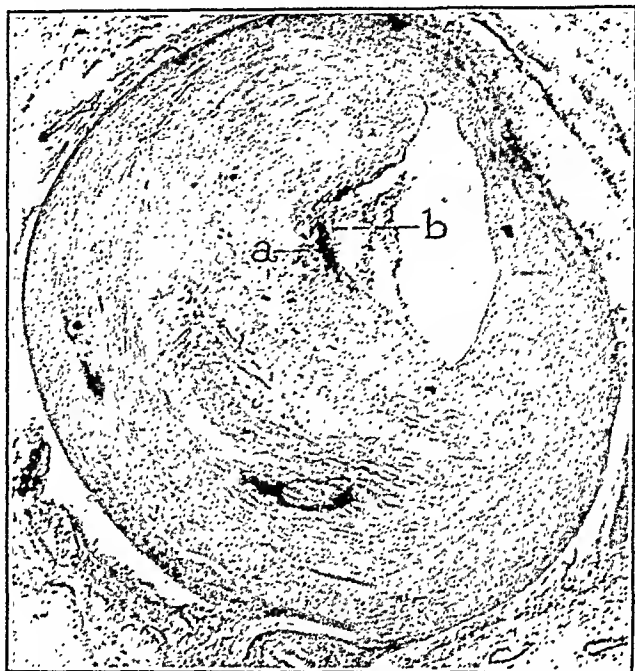


Fig. 1.—Case 5542. A section through the edge of the occluded portion of the right coronary artery, showing several recent hemorrhages, *a*, in the intima. The endothelial lining, *b*, is intact.



Fig. 2.—Case 5542. A section 1 mm. distal to Fig. 1. The hemorrhages, *a*, are covered by endothelium, *b*, but bulge into the lumen.

hemorrhage just beneath the intimal endothelium which at no point was ruptured (Figs. 1, 2, 3, and 4). There was no thrombosis, but the vessel was completely occluded by the large hematoma.

CASE 5561.—A white male, 43 years of age, a press operator, stated that ten days before admission to the hospital he was suddenly stricken with crushing sub-

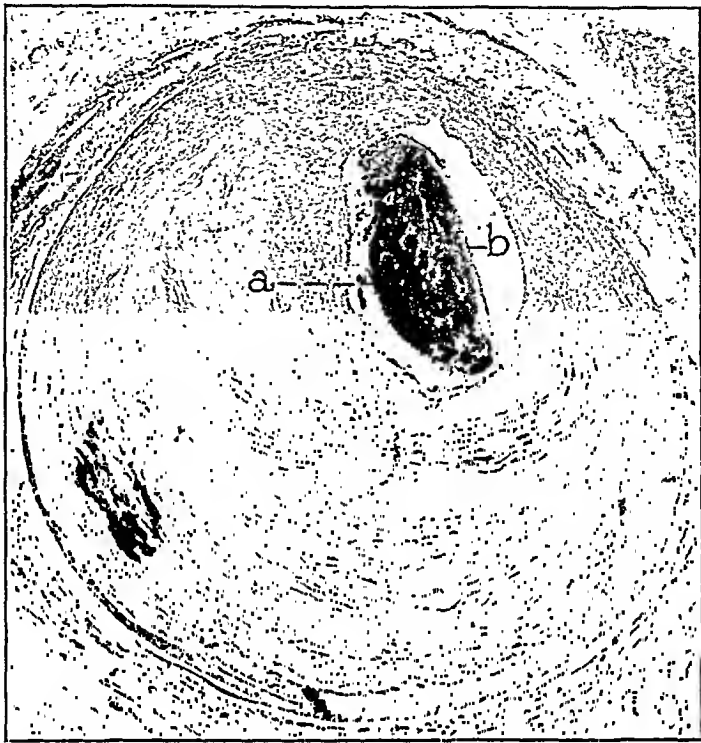


Fig. 3.—Case 5543. A section 4 mm. distal to Fig. 1. A large hematoma, *a*, is present, which has obstructed the lumen. The endothelial lining, *b*, is intact.

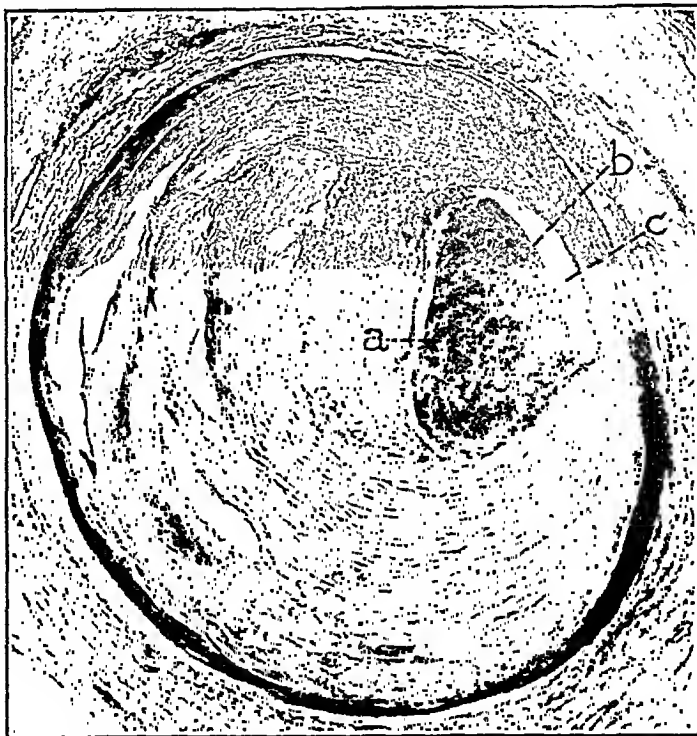


Fig. 4.—Case 5543. Occlusion of the lumen, *c*, by the subendothelial hematoma, *a*. A section 5 mm. distal to Fig. 1.

sternal pain which radiated to both shoulders and down the arms. The pain re-
 curred at irregular intervals. His mother had died at 52 years of age of a cerebral
 hemorrhage.

The blood pressure was 118/88 but dropped to 85/55 shortly after admission to the hospital. The temperature was 37.5° C., the pulse 92, and the respirations 16. There was slight dyspnea. Although distant, the heart sounds were distinct, and a short time after admission a loud pericardial friction rub appeared. The white blood cell count was 14,650, with a preponderance of polymorphonuclear neutrophils. On two occasions an electrocardiogram showed evidences of infarction of the anterior and apical portions of the left ventricle. During his hospital stay the patient continued to have severe pain, and on the thirteenth day he suddenly developed great gasping respirations and died. The heart sounds were muffled, as though from ventricular fibrillation. Death occurred twenty-three days after the onset of symptoms.

At autopsy the heart weighed 480 gm. There was massive, recent infarction of the anterior and apical regions of the left ventricle, the apex of the right ventricle, and approximately two-thirds of the anterior portion of the interventricular septum. The apex of the left ventricle bulged markedly to form an aneurysm 5 cm. in diameter which was filled with fresh thrombus.

One centimeter below the origin of the descending ramus of the left coronary artery was a soft, dark red blood clot which completely filled the lumen. Serial sections through this lesion revealed a large atheromatous plaque in which recent hemorrhage had taken place with the formation of an occluding hematoma. There was no thrombosis.

CASE 5584.—A white male, 55 years of age, was a business man, and, so far as his family and friends were aware, had been in good health until the day of death when he was shaken up in a slight accident. He was carefully examined by a physician immediately after the mishap and was thought to be unharmed. Six hours later he was found dead.

At autopsy moderately severe sclerosis of all branches of the coronary arteries was discovered. In the descending ramus of the left coronary artery, 3 cm. from its origin, was found a massive, annular hemorrhage in an atheromatous plaque, thus forming a large hematoma which completely occluded the lumen of the vessel. The hemorrhage was recent, with well preserved red blood cells, and the inner lining of the intima was everywhere intact (Figs. 5 and 6). There was no myocardial infarction.

CASE 5840.—A 48-year-old white woman, a housewife, was known to have had diabetes for five years. Twenty-two maternal relatives had had diabetes mellitus. Six months before her fatal illness the patient first complained of substernal pain, dyspnea, and edema on exertion. An electrocardiogram taken at this time was normal. She continued to have frequent attacks of anginal pain which were relieved only partially by nitroglycerin. Twelve hours before admission, following a profound emotional experience and after a ten-day period of intermittent precordial pain, the patient was seized with severe, excruciating, substernal pain which did not radiate and was not relieved by nitroglycerin.

The blood pressure was 140/85, the temperature 37.6° C., the pulse 120, and the respirations 35. The patient was obese, dyspneic, and slightly cyanotic, with quiet heart sounds and a regular pulse. The leucocyte count was 10,100, with a normal differential count. The electrocardiogram, taken on the day of admission, showed indications of myocardial damage with interventricular block, and sinus tachycardia, which were thought to indicate a posterior basal infarct with involvement of the interventricular septum. The patient's condition became steadily worse, and she died twelve days after the onset of the final attack.



Fig. 5.—Case 5584. A section through the descending branch of the left coronary artery, showing massive hemorrhage, *a*, into the vessel wall. The endothelial lining, *b*, is intact, and the lumen, *c*, is patent.

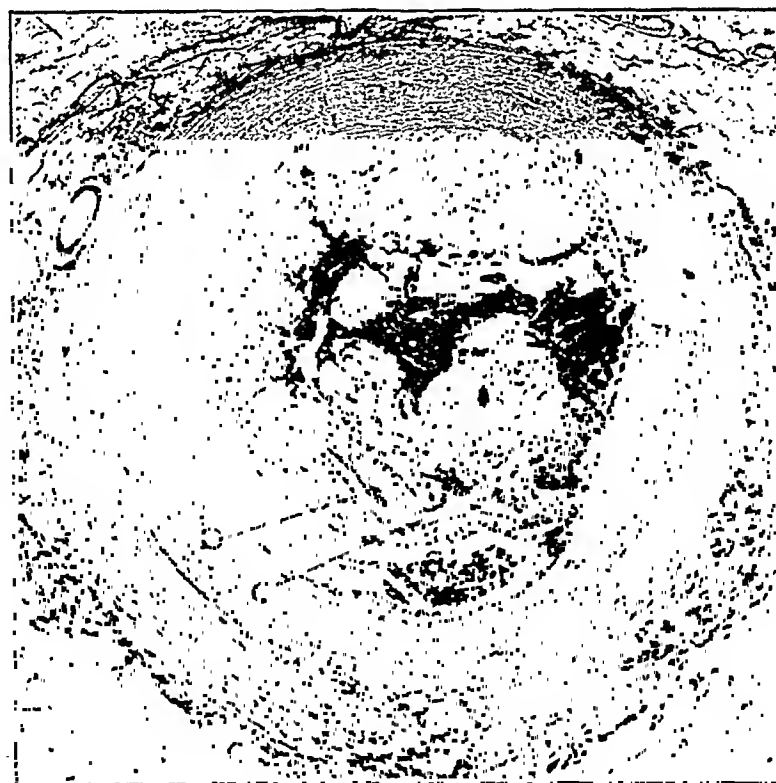


Fig. 6.—Case 5584. A section 3 mm. distal to Fig. 5. The lumen, *c*, is occluded because of compression by the intramural hemorrhage, *a*. The endothelial lining, *b*, is intact, and there is no thrombus.

At autopsy the heart weighed 335 gm. There was a recent, superimposed upon an organizing, infarct involving the left ventricle, particularly the posterior aspect, from the base to the apex and the posterior portion of the interventricular septum.

The left circumflex coronary artery was completely occluded by soft, dark red blood clot at a point 2 cm. from its origin. Serial sections showed massive recent hemorrhage into the wall of the artery with the formation of a hematoma which completely obliterated the lumen. The endothelial lining of the intima was everywhere intact, and there was no thrombosis. Both coronary arteries were the seat of severe sclerosis.

CASE 5928.—A 53-year-old negro, a laborer, had complained for nine months of shortness of breath and pain in the left upper quadrant. Fifteen years before the first admission a diagnosis of aneurysm of the transverse and descending portions of the aorta had been made. The Wassermann reaction was positive at that time. During the intervening years he was treated in the Out-Patient Department and was able to do the hard work of a laborer. He was also known to have diabetes mellitus, which responded well to treatment,

On admission to the hospital the blood pressure was 155/125, the temperature 38.6° C., the pulse 100, and the respirations 36. The patient was well developed and well nourished and did not appear seriously ill. The heart was greatly enlarged to the left, and two apical impulses were noted in the posterior axillary line, one in the fourth and the other in the fifth costal interspace. The blood and spinal fluid Wassermann tests were negative at this time although the Kline exclusion test was two-plus. X-ray examination indicated the presence of an aortic aneurysm.

An electrocardiogram showed that, since a record taken five years before, there had appeared changes in the S-T interval and T-waves of Leads I and III and more marked left axis deviation. These changes together with slurring of the QRS complex in Lead I and notching in Lead II were interpreted as indicating myocardial damage.

Three days before death the temperature increased to 40.4° C., the patient developed marked Cheyne-Stokes respiration and became disoriented. Signs of bronchopneumonia appeared in the right lung and the leucocyte count rose to 12,500. He died thirty-five days after admission to the hospital.

At autopsy the heart was greatly enlarged, and there was a fusiform and saccular aneurysm of the descending thoracic portion of the aorta with displacement of the heart, lungs, and esophagus. The aneurysmal sac was completely filled by thrombus—the so-called spontaneous cure.

The circumflex branch of the left coronary artery was occluded by soft, brownish red material at a point 2 cm. from the ostium. Serial sections through this area showed recent intramural hemorrhage with obliteration of the lumen by the resulting hematoma. The intimal endothelium was everywhere intact, and there was no thrombus.

In the right coronary artery, 5 cm. from the ostium, was an intramural hemorrhage which did not completely occlude the lumen but reduced it to an opening 1.5 mm. in diameter.

There was no evidence of recent myocardial infarction although occasional areas of fibrosis were encountered.

CASE 5929.—A white man, 62 years old, a picture framer, had complained for one week of transient attacks of severe precordial pain which radiated to the shoulders. During these attacks the patient noticed that he was short of breath.

The blood pressure was 190/100, the temperature 36.8° C., the pulse 60, and the respirations 40. The day before admission to the hospital the blood pressure dropped to 110/70, and the temperature increased to 39° C. The patient was suffering severe pain and was very apprehensive. Although the heart sounds were weak, they were regular and no murmurs were heard. There were no signs of congestive heart failure.

An electrocardiogram taken a few hours after admission to the hospital showed notching and slurring of the QRS complexes and elevation of the S-T intervals in Leads II and V. On the next day another record showed a decrease in the voltage of the QRS complex. The S-T interval in Leads I, IV and V had become elevated with inversion of the T-wave in Leads I and V. These changes were considered diagnostic of recent infarction of the anterior and apical portions of the left ventricle. During the following six days two other electrocardiograms were made. They showed a further decrease in the voltage of the QRS complex, with inversion of the T-wave in Leads II and III, and a decrease in the degree of inversion of the T-wave in the chest lead. These changes were considered consistent with the course of infarction of the apex and anterior wall of the left ventricle.

About three weeks after the onset of the illness, a pericardial friction rub developed and the leucocyte count rose to 13,700. The next day the patient became cyanotic, had a convulsion, and died.

At autopsy the heart weighed 530 gm. A large wedge-shaped mass of infarction was found in the anterior wall and apex of the left ventricle and the apical portion of the interventricular septum. Mural thrombus covered the necrotic myocardium.

The coronary arteries were the seat of severe sclerosis. One centimeter from its origin the lumen of the descending branch of the left coronary artery was very greatly reduced by an atheromatous plaque and occluded by dark red, friable material which seemed to have its origin in the plaque. The artery was occluded for a distance of nearly 1 cm. Microscopic sections through this region showed a large intramural hematoma which was undergoing organization. There was no thrombus.

CASE 5814.—A white male, 54 years of age, unemployed, but formerly a janitor, was well until three hours before admission when he awakened with severe stabbing pain, which originated substernally and radiated to the left shoulder, leaving the arm numb. The pain was continuous. In 1913 he had been told he had a leaky heart and noticed some dyspnea on mild exertion, but he had been able to work without difficulty.

The patient was prostrated, pale, sweating profusely, and complained of a sense of impending doom. The blood pressure was 80/30, the temperature 37.8° C., the pulse 77, and the respirations 22. The heart was weak and irregular, with quiet, distant sounds. There was marked dyspnea and ashen gray cyanosis. Three hours after admission the patient died while talking to the interne.

At autopsy the heart weighed 450 gm. The coronary arteries were the seat of severe sclerosis. Two centimeters from the ostium of the right coronary there was an ulcerated atheromatous plaque, 1 cm. in length, which on section oozed soft brownish red material and almost completely occluded the lumen. Serial sections showed massive recent hemorrhage into an atheromatous plaque (Fig. 7). At one point the intima was interrupted, and a small mural thrombus had formed (Fig. 8). The lumen was almost completely occluded by the hematoma and the mural thrombus. The myocardium showed a mild degree of fibrosis but no evidence of recent infarction. There was a moderate amount of fat infiltration in the right ventricle.

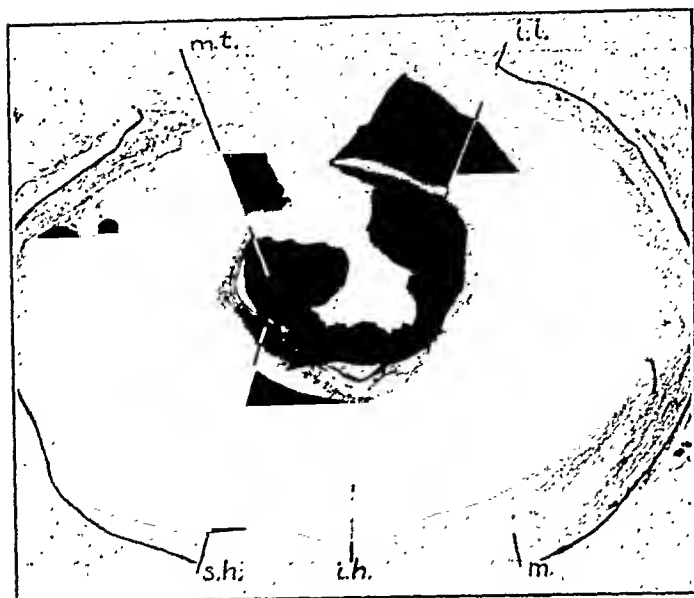


Fig. 7.—Case 5814. Diagram to illustrate the lesions found in the stenosed portion of the right coronary artery. At this level the intramural hematoma is covered by a narrow, intact layer of intima.

m.t., mural thrombus; *i.i.*, intact intima; *s.h.*, subendothelial hemorrhage; *i.h.*, intramural hematoma; *m.*, media.

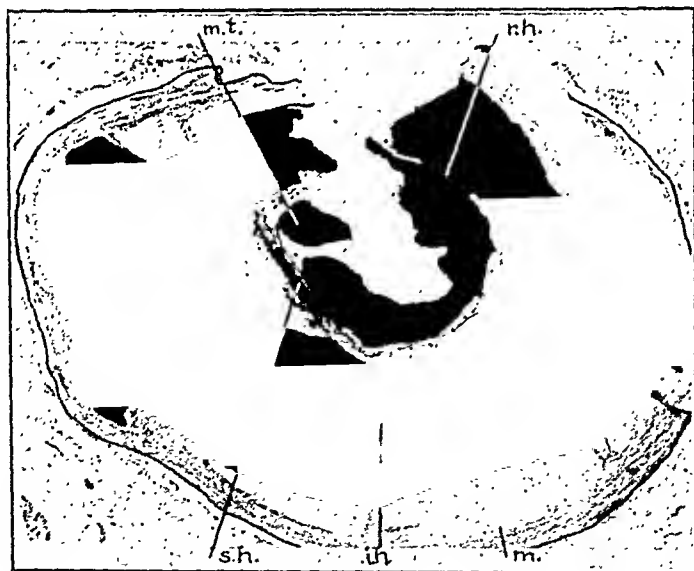


Fig. 8.—Case 5814. Diagram of a section of a few millimeters distal to Fig. 7, showing disruption of the intima.

m.t., mural thrombus; *r.h.*, rupture of hematoma into arterial lumen; *s.h.*, subendothelial hemorrhage; *i.h.*, intramural hematoma; *m.*, media.

SUMMARY OF FINDINGS

The clinical findings in these seven cases were for the most part those of myocardial infarction and coronary thrombosis. Most of the patients were in the sixth decade. One patient was a white woman and another a negro, but the others were white males. Many of the patients belonged to the laboring classes, although various occupations were represented. One-half of the patients had previously suffered from angina pectoris, but none had had symptoms for longer than ten months, and all died within five weeks of the onset of the final attack. Death occurred suddenly and unexpectedly in two patients (Cases 5584 and 5814), but with these exceptions all complained of precordial pain radiating to the arms. The usual signs and symptoms of myocardial infarction were present. Electrocardiographic records were obtained for five of the patients, and in these cases myocardial damage was shown by changes in configuration of the QRST deflections. In two cases it was possible accurately to localize the infarction (Cases 5561 and 5840). However, there were no characteristic electrocardiographic findings which permitted differentiation between intimal hemorrhage and true thrombosis.

The pathologic findings were similar in the seven cases. Severe intimal sclerosis with calcification and the formation of large atheromatous plaques were constant features. The lumen of one or more of the branches of the coronary arteries was blocked by soft, dark red blood clot, and serial sections of these areas revealed that the occlusion was not caused by thrombosis, as had been supposed on gross examination, but by hemorrhage into the wall of the artery. The hemorrhage was usually found in an atheromatous plaque (four cases) and except for one (Case 5814) was covered by a layer of intact endothelium. In no case was there bleeding into the media. The size of the hemorrhage varied but was usually massive, causing stenosis by actual compression of the lumen of the affected artery. In addition to the large hematoma, there were often multiple small hemorrhages scattered throughout the intima, especially beneath the endothelium. The intima in the region of the hemorrhage was always richly vascularized by capillaries which were frequently surrounded by focal accumulations of red blood cells. The age of the hematoma could not be accurately determined, but in many cases the excellent preservation of erythrocytes indicated recent origin. Sometimes, however, there was lysis of the red blood corpuscles and beginning organization and pigmentation.

Case 5561 illustrates a combination of lesions which was frequently observed in cases of coronary occlusion, namely, intramural arterial hemorrhage and recent thrombosis. The massive hemorrhage into an atheromatous plaque was easily made out (Fig. 7) and in most of the sections there was a narrow border of intact intima, separating the intramural hematoma from the lumen, but at one point the hemorrhage

had broken through the intima (Fig. 8). Thus, in addition to the large intramural hematoma, there was a recent thrombus within the lumen of the vessel. The significance of this combination of lesions will be discussed later in the paper.

An analysis of the incidence of the lesion in the various branches of the arteries shows that both arteries were involved in one case, the left coronary artery in five and the right in three cases. The commonest site of occlusion in the left coronary artery was just distal to the origin of the anterior descending branch (three cases). In one case it was in the circumflex branch near the midpoint. The right coronary artery was most frequently involved in the middle third (three cases).

The lesions produced in the myocardium were variable. Four cases showed recent infarction of the myocardium. The diseased muscle was easily recognized in the fresh specimen, and the usual histologic appearance of recent infarction was present. In three of the hearts there was no demonstrable myocardial infarction. This finding is explained in two cases by the fact that the patients died suddenly so that sufficient time had not elapsed for infarction to develop.

DISCUSSION

Although the finding of intramural arterial hemorrhage is an old observation, the lesion has received but little attention from most writers. Such hemorrhages are most commonly seen in the wall of the aorta but may affect any vessel. Recently Paterson¹ studied the vascularization and hemorrhage in the intima of arteriosclerotic coronary arteries and found hemorrhagic lesions within the intima in atheromatous foci in a number of arteriosclerotic coronary arteries, including those from nine patients with recent coronary thrombosis. He was able to demonstrate vascularization of the intima by discrete capillaries arising from the lumens of sclerotic coronary arteries and noted that when this intramural "hemorrhage was recent, capillary channels were found in the inner layers of the intima in close proximity to the extravasated blood."

Previously Benson² and Koch and Kong³ had described breaks in the integrity of the intima of thrombotic coronary arteries permitting escape of blood between or into the coats of the artery and suggested that such changes might lead to the formation of a thrombus. Leary^{4, 5} described the rupture of an atheromatous mass into the lumen of a coronary vessel with secondary thrombus formation. He has also described intimal capillaries arising directly from the lumen of the artery. Clark, Graef and Chasis⁶ examined serial sections of eleven thrombotic coronary arteries. "The common observation was the presence of a fresh break in the fibrous lining of a lipoid plaque with penetration of blood elements into the atheroma. In other instances thrombus formation occurred on

an atheromatous plaque, in which thinning out and separation of the collagenous fibers of the lining plaque also had permitted infiltration of blood elements."

Despite the fact, however, that intramural arterial hemorrhage has been frequently observed, the actual occlusion of a coronary artery by a hematoma formed entirely within the wall of the vessel and without thrombosis has not been previously described. In the gross this lesion is not easily recognized and might be interpreted as a thrombus. Even the microscopic examination of a few sections might not lead to the correct diagnosis. It is often necessary to examine serial sections through the whole of the occluded portion of the vessel in order to determine whether or not the intima is intact and whether the hemorrhage is entirely within the wall. When such a lesion is old and the only residuum is hemosiderin in an atheromatous plaque, the lesion could be misinterpreted as a canalized and organized thrombus.

In the present study serial sections of 41 occluded coronary arteries were studied, and of these, six (14.6 per cent) were caused solely by intramural hematoma. Fourteen (34.2 per cent) of the other cases showed a combination of intramural hemorrhage and thrombosis and one of these is included in this report because it illustrates the difficulty of determining whether the thrombosis is secondary to the rupture of a hematoma or whether the hematoma is the result of rupture of the intima and extravasation of blood beneath it. Several points, however, indicate that the former explanation is the correct one. If it be assumed that the thrombus formed first, then it is difficult to explain the formation of a hematoma in the wall of a vessel because, if the occlusion were complete, no blood could reach the affected portion or, if the occlusion were only partial, it would seem logical to assume that the mural thrombosis would protect the intima and tend to prevent the development of a hematoma. Again in some of the cases which have been studied, the hemorrhage within the vessel wall is of greater age than the thrombus, as indicated by the finding of hematogenous pigment within phagocytes and of beginning organization, whereas the thrombus shows none of these features.

It is no longer necessary to assume that bleeding into the wall of an artery is due solely to rupture of the intima and dissection beneath it by the blood stream, for Paterson¹ and Leary^{4, 5} have convincingly demonstrated the origin of intimal capillaries from the lumen of a sclerotic artery. This finding has been confirmed by the present study, and it has also been possible to demonstrate vascularization of the atheromatous plaques by capillaries derived from the adventitia. It is easy to conceive that capillaries within an atheromatous plaque may rupture, for the soft, easily compressible material of the atheroma offers no support against the capillary blood pressure. Since patients with coronary arteriosclerosis frequently have hypertension, a small intramural capil-

lary might readily be ruptured and form a hematoma. With time such a hematoma could easily become large enough completely to close the lumen or even to rupture.

The site of rupture of a hematoma into the lumen of an artery would no doubt afford an excellent nidus for the development of a secondary thrombus. It has not been possible to demonstrate this convincingly, although many of the cases suggest strongly that the thrombus is secondary to a ruptured intramural hemorrhage. Winternitz, Thomas, and Le Compte⁷ have recently suggested that hemorrhage derived from the intramural circulation may be an important factor in the development of arteriosclerosis. Further study may elucidate this problem.

SUMMARY

Six cases are described of complete occlusion of sclerotic coronary arteries by intramural arterial hemorrhage without thrombosis. An additional case is presented in which there was a combination of intramural hemorrhage and thrombosis of the left coronary artery. Death was directly attributable to the coronary lesion in all cases although in three there was no myocardial infarction. Attention is called to the probable importance of intramural arterial hemorrhage in the pathogenesis of coronary thrombosis.

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A STUDY OF ELECTRICAL ACTIVITY IN THE AURICLES*

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CONSIDERABLE data have been accumulated regarding the electrocardiographic effects of myocardial damage and aberrant excitation in the ventricles during the past few years. In contrast, however, the present knowledge regarding similar conditions in the auricles is rather scant. As yet no reports have appeared, to our knowledge, describing the electrocardiographic changes resulting from experimental injury to the auricular myocardium; and there is some controversy concerning the relationship of the site of ectopic excitation in the auricle to the form of the resulting aberrant P-wave.

Recently the subject of duration of electrical activity in the auricles has received renewed attention. As pointed out by Wedd and Stroud,¹ the onset of the P-wave heralds only approximately the initiation of the period of invasion, for a low grade electrical potential difference indicating activity in the vicinity of the S-A node exists before this inflection is inscribed. Further, the termination of the P-wave can no longer be considered to represent the completion of the period of electromotive changes, since a deflection has been described following the P-wave, which has been proved to be bound up with electrical recession in the auricles. This deflection, designated as the Ta wave by Hering,² is generally opposite in direction to the P-wave, but is usually obscured by the aftercoming ventricular complexes.

In the present investigation, it was therefore decided to study the electrocardiographic changes resulting from (a) cauterization of various sites on the auricular wall, and (b) the production of artificial premature auricular contractions. It was hoped that by comparing the curves resulting from the two procedures a correlation might be found to exist analogous to that observed in our study of the ventricles under similar conditions.†^{3, 4} Further, it was thought that by the introduction of a constant current of injury (as a result of cauterization) some information might also be obtained as to the actual duration of electrical events in the auricles. With this point in mind, and to obliterate possible

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‡In the case of the ventricles, it was found that the direction of the initial main deflection of the extrasystolic wave was inversely related to the direction of the RST deviation obtained with normal sinus rhythm, when the site on the ventricle from which the premature contraction arose was subsequently cauterized.

electrocardiographic changes caused by the presence of ventricular complexes, it was decided to produce complete heart-block in several of the animals prior to cauterization.

The data obtained by the above procedures form the basis for this report.

METHOD

The following data were obtained from experiments on six cats and five dogs, anesthetized by "dial" injected intraperitoneally (0.6 c.c. per kilo). Artificial respiration was instituted, the sternum and portions of adjoining ribs and cartilages

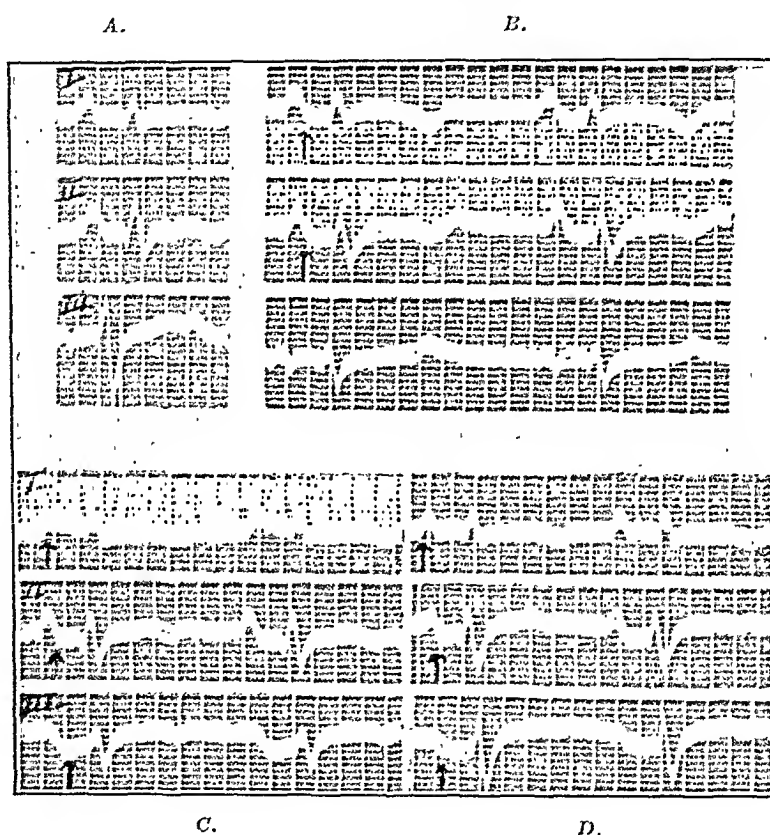


Fig. 1.—Cauterization of auricles in the dog (dog 1). *A*, Control records, *B*, Cauterization of right auricle. Depression of P-Ta interval in Leads I and II and no change in Lead III. *C*, Cauterization of left auricle about ten minutes after "B." Elevation of P-Ta interval in Lead I and depression in Leads II and III. *D*, Cauterization of both auricles about twenty minutes after "C." P-Ta interval back in normal isoelectric position in Lead I and depressed in Leads II and III. Arrows indicate changes in position of P-Ta interval. Vertical time lines—0.04 second.

were removed, and the entire heart was exposed by slitting the pericardium. The cut edges of the latter were then sewed to the chest wall so as to form a hammock and thus maintain the heart in a constant experimental position. Control electrocardiograms were obtained before opening the chest and after exposing the heart. In some experiments first one and then the other branch of the Bundle of His were cut in order to induce complete heart-block. In all but two cases, a cautery was applied to specific portions of the auricles so as to produce an injury which extended as deeply as possible into the auricular wall without penetration of the cavity. After the lesion was produced, cotton pads were placed lightly over the

heart, the sternum was replaced and an electrocardiogram was immediately taken. If no obvious change was noted, the cauterized area was extended until definite alterations were observed. In most experiments it was found possible to reapply the cautery later to a different site in the auricular wall for further observations.

Prior to cauterization, in four of the experiments on dogs, premature auricular contractions were elicited by stimulating various sites on the auricles with single minimal induced shocks sent in at different times in the cardiac cycle.

Since all complexes in Lead I were generally of low amplitude, it was decided to increase the sensitivity of the string so that the introduction of one millivolt caused a deflection of two centimeters. The other two leads were obtained with conventional standardization, i.e., 1 cm. = 1 mv.

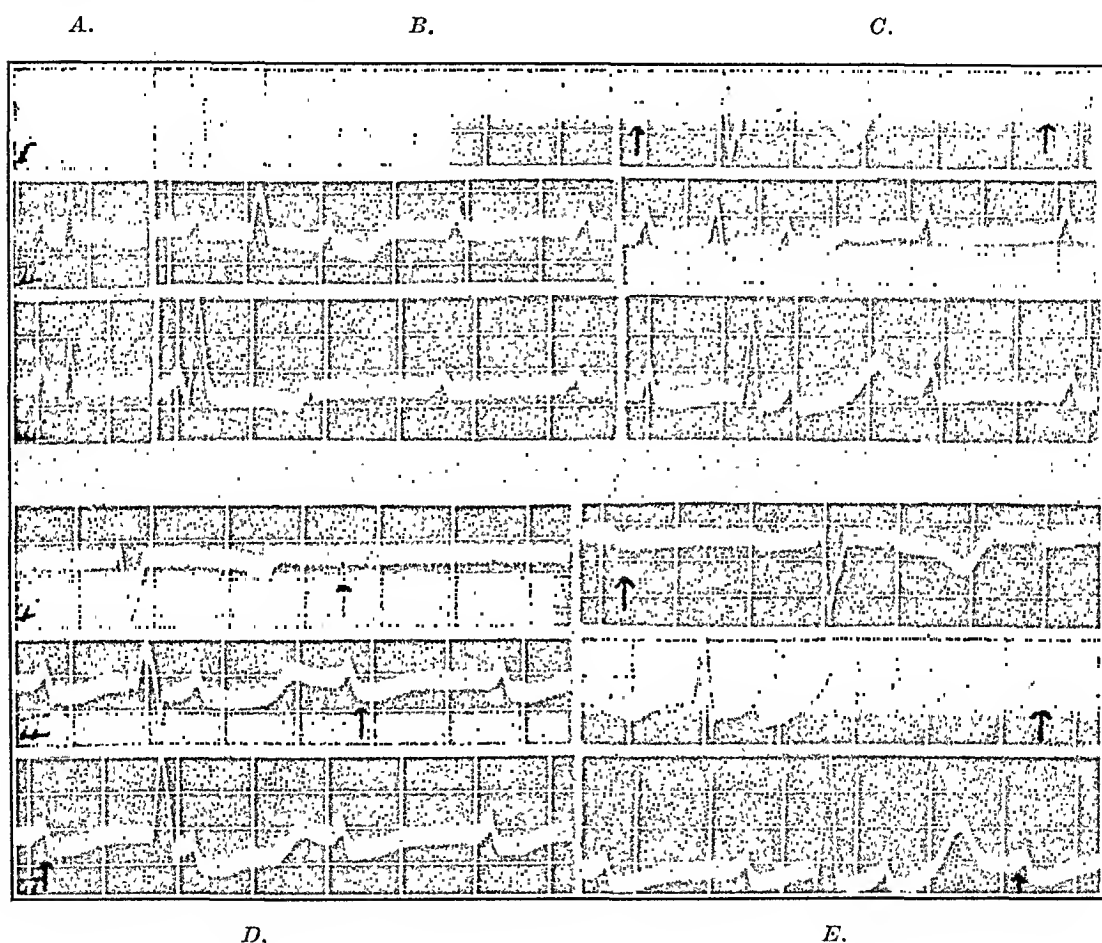


Fig. 2.—Cauterization of auricles in the cat (cat 1). *A*, Control record. *B*, Complete heart-block produced by cutting first the right and then the left branch of the Bundle of His. *C*, Cauterization of the left auricle. Elevation of P-Ta interval in Lead I and no change in Leads II and III. *D*, Cauterization of both right and left auricles. P-Ta interval back in normal isoelectric position in Lead I and markedly depressed in Leads II and III. *E*, Further cauterization of right auricle about ten minutes after "D." Depression of P-Ta interval in all three leads. Arrows indicate changes in position of P-Ta interval. Vertical time lines—0.2 second.

RESULTS

I. Cauterization of Auricular Wall

Upon cauterization of the auricular wall, an elevation or depression of the normally isoelectric interval between the end of the P and the beginning of the R-wave was consistently noted (Figs. 1 and 2). This portion of the electrocardiogram (which may be considered to be the

counterpart of the RS-T segment of the ventricular grouping) will hereafter be designated as the P-Ta segment, since it lies between the P-wave, which indicates auricular excitation, and the Ta-wave (obscured by the R-wave) which indicates auricular retreat. Conformity is thus maintained with ventricular terminology.

In many cases the P-wave was affected by the cauterization as well as the P-Ta segment, although not as conspicuously (Fig. 1). The modifications of the P-wave consisted either of an increase or decrease in its height, with slight changes in contour. In those records in which an

TABLE I

EXPERIMENT NUMBER	AURICLE CAUTER- IZED	EFFECT OF CAUTERIZATION UPON P-Ta INTERVAL			DURATION OF P-R INTERVAL BEFORE COMPLETE HEART-BLOCK	DURATION OF P-WAVE AND P-Ta CHANGE AFTER INJURY, IN THOSE CASES WITH COM- plete HEART-BLOCK
		LEAD I	LEAD II	LEAD III		
Cat 1-A	Left	+	0	-	.08 second	.18 second
Cat 1-B	Right and Left	0	=	=	.08 second	.21 second
Cat 1-C	Right	-	=	=	.08 second	.23 second
Cat 2	Left	+	-	-		
Cat 3-A	Right	=	=	=		
Cat 3-B	Left	+	-	=		
Cat 4-A	Right	-	0	0		
Cat 4-B	Left	+	-	-	.06 second	.12 second
Cat 5	Left	+	-	-	.09 second	.15 second
Cat 6	Right and Left	+	-	-	.08 second	.17 second
Dog 1-A	Right	-	-	0		
Dog 1-B	Left	+	-	=		
Dog 1-C	Left and Right	0	=	=	.09 second	.14 second
Dog 2-A	Right	=	=	-		
Dog 2-B	Left	+	=	=		
Dog 3-A	Right	0	-	-		
Dog 3-B	Left	+	=	=	.08 second	.13 second

+ P-Ta segment displaced in a positive direction.

- P-Ta segment displaced in a negative direction. The number of these represents the relative magnitude of the displacement.

0 No effect upon the P-Ta segment.

elevation of the P-Ta segment was present, the downstroke of the P became fused with the first portion of the P-Ta segment (Fig. 1-C); in a manner similar to the change observed in the ventricular curve following ventricular trauma (the R-T transition arising high up on the descending limb of the R-wave). When a depression of the P-Ta interval was present, it was generally written only after the descending limb of the upright P-wave had crossed the isoelectric line (Fig. 1-B). In cases where the P-wave was small and the P-Ta change comparatively greater, the P-wave often lost its identity in the latter (Fig. 2-C).

Changes in Lead I.—Examination of Table I reveals that in all instances, following cauterization of the left auricle, the P-Ta interval in Lead I became elevated from its previous isoelectric position (Figs. 1-C and 2-C) while in all instances of cauterization of the right auricle (except in one case in which no change was manifest) a depression of the P-Ta interval was obtained (Figs. 1-B and 2-E) in that lead. Changes in the site of the trauma, so long as it was limited to the same auricle, did not affect these results. Thus cauterization of either the anterior or posterior surface of the right auricle uniformly produced a depression of the P-Ta segment, while cauterization of comparable sites in the left auricle caused an elevation of the P-Ta segment.

Further evidence on the relationship of site of trauma to the electrocardiographic alteration in Lead I was observed in two experiments (cat 1 and dog 1) in which first one, and then the other, or both auricles were successively injured. In one (dog 1 in Fig. 1) with cauterization of the right auricle, there was a depression of the P-Ta segment in Lead I, which was followed by a reversal to an elevated position when the left auricle was subsequently injured. After a twenty-minute interval, both auricles were again simultaneously cauterized, whereupon the P-Ta segment returned to an isoelectric position. In the other instance (cat 1 in Fig. 2) the left auricle was first cauterized, with a consequent elevation of the P-Ta segment in Lead I, which then became isoelectric when this procedure was applied to both auricles. Following this with more extensive cauterization of the right auricle, a depression appeared. In both cases the return of the P-Ta segment to the isoelectric line with simultaneous cauterization of the two auricles apparently was not due to a disappearance of the transient current of injury (for at the same time Leads II and III in each instance manifested definite indications of its presence (Figs. 1-D and 2-D), but rather to the neutralizing effect of the electrical disturbances produced in one auricle upon those consequent to cauterization of the other. One is justified in stating, therefore, on the basis of the above, that the site of cauterization, as to the right or left auricle, will determine the type of alteration of the P-Ta segment observed in Lead I.

Changes in Leads II and III.—The changes in Leads II and III, upon cauterization of either auricle, uniformly consisted of a depression of the P-Ta segment, regardless of whether the anterior or the posterior surface was the site of the lesion (Figs. 1 and 2). In rare instances, no alterations were noticed in these leads, despite changes in Lead I; the reverse also being true in other cases. No localizing signs could therefore be obtained from an examination of the changes in the position of the P-Ta segment in Leads II and III.

Comparison of the Normal P-R Interval With the Combined Duration of the P-Wave and P-Ta Displacement Change in Complete Heart-

Block.—With normal sinus rhythm following auricular cauterization, the P-Ta displacement was seen to end abruptly with the onset of the more prominent QRS complex. In order to determine whether or not the displacement actually persisted beyond the ventricular complex, complete heart-block was produced in four cats and two dogs (Table I), and the normal P-R interval was then compared with the combined duration of the P-wave and P-Ta displacement change, after the injury. Whereas the P-R interval in the cat and dog ranged between 0.06 and 0.09 second, the combined P-wave and P-Ta deviation ranged between 0.12 and 0.23 second (Fig. 2) or much longer than the P-R interval. The significance of these findings will be discussed later.

II. Production of Auricular Premature Contractions

Changes in Lead I.—In four experiments on dogs, premature auricular contractions were elicited from various sites on the epicardial surface of both auricles prior to cauterization of one of these sites. It was found that on stimulation of the right auricle the aberrant P-wave in Lead I was almost consistently positively directed (Fig. 3). This held for sites on the anterior, lateral, and posterior surfaces, as well as for superior, middle, and inferior levels, the only exception being one instance of stimulation on the lateral surface inferiorly from which a diphasic P-wave was obtained. In each of the four experiments eight sites on the right auricle were examined.

On stimulation of the left auricle, the aberrant P-wave in Lead I was generally negative (Fig. 4), although in a number of instances it was difficult to decide upon its exact direction because of small amplitude or distorting effects of the "stimulus escape." Sites on the anterior, lateral, and posterior surfaces at different levels were likewise studied. In one experiment, ten areas were stimulated and in all cases in which the results were decisive (six) they conformed to the above generalization. This was also true in the other three experiments in each of which six areas were examined.

Changes in Leads II and III.—The aberrant P-waves in Leads II and III resulting from stimulation of the right and left auricles, while infrequently variable, were usually positively directed for all sites on both auricles (Figs. 3 and 4).

III. Comparison of Curves Produced by Auricular Trauma and Premature Contractions

The results of the subsequent cauterization of the auricles in two of the last described experiments conformed with the findings already described (Table I). Comparison of the electrocardiographic records of the two procedures (i.e., first the production of ectopic auricular

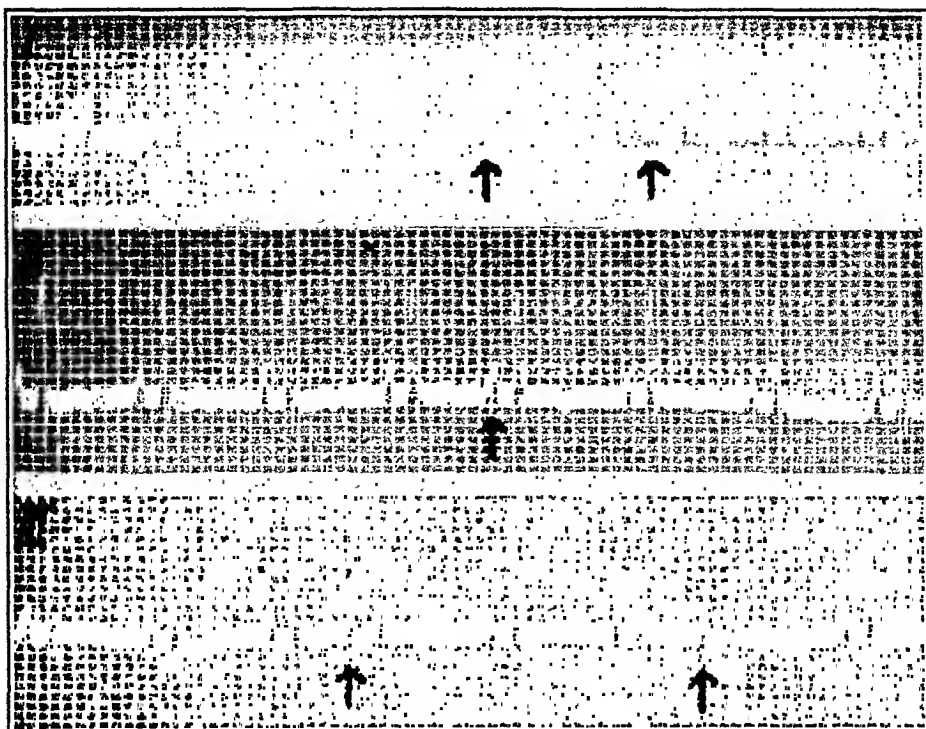


Fig. 3.—Auricular premature contractions produced by stimulation of right auricle in the dog. Arrows indicate the aberrant P-wave followed by a supraventricular complex and under compensatory pause. The aberrant P-wave is upright in all three leads. Vertical time lines—0.04 second.

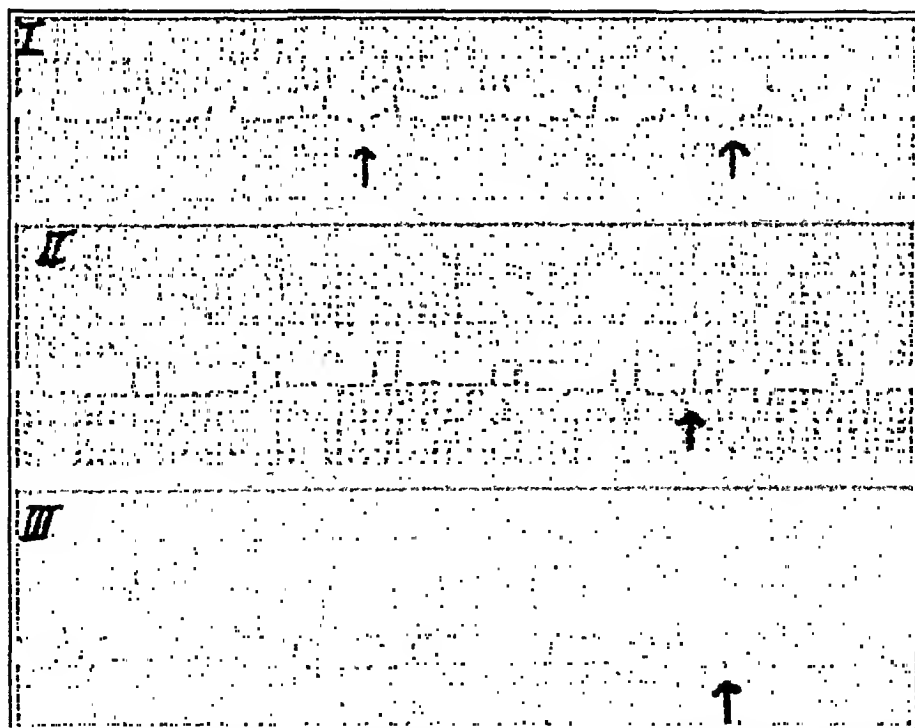


Fig. 4.—Auricular premature contractions produced by stimulation of the left auricle in the dog. Arrows indicate the aberrant P-wave followed by a supraventricular complex and under compensatory pause. The aberrant P-wave is inverted in Lead I and upright in Leads II and III. Vertical time lines—0.04 second.

beats from a specific site and then cauterization of this site) revealed that whereas the aberrant P-waves in Lead I were positively directed for sites on the right auricle, the displacement of the P-Ta interval (with normal sinus rhythm) following cauterization of this auricle was negatively directed. A similar type of relationship held for the left auricle, except that here the direction of the aberrant P-wave was negative and the P-Ta segment positive. In reference to Lead II and Lead III, the P-Ta interval was generally depressed for sites of trauma on either right or left auricle, while the aberrant P-waves were positively directed. The significance of these findings will be discussed.

DISCUSSION

It is generally conceded that when the ventricular myocardium is traumatized, the resulting current of injury manifests its presence by a displacement of the RS-T segment from its normally isoelectric position. Actually, of course, this change represents a temporary negative variation of the injury current, i.e., a tendency toward the neutralization of that current when the charges of normal excitation are present in the intact muscle surrounding the injured region. Although the negative variation of the current of injury exists from the beginning of activation to the end of recovery, the QRS complex is very little affected because of its relatively greater electrical magnitude, and thus the only obvious change is seen in an alteration of the RS-T segment and possibly a distortion of the T-wave as well.

From an examination of the present results, parallel conclusions to the above can be drawn for the electrocardiographic representation of auricular electrical events. First, to discuss the normal curve, there is a wave which can be considered roughly to indicate the onset of invasion, the P-wave, which is followed by an isoelectric interval, the P-Ta segment, during which period there is a state of balanced activity or temporary neutralization of potential differences throughout the auricles. The period of retreat or recovery is then represented by the Ta-wave, but since the electrical events during this stage are of small magnitude, the wave is either lost in the much greater electrical effects consequent to activation of ventricular muscle, or if written before the latter takes place, it is of such small amplitude as to be generally invisible. However, if auricular muscle is traumatized, a factor is introduced which tends to alter the relationship and contour of the waves so long as the tissue remains in a dying state. For now normal excitation of auricles injured locally results in a negative variation of the existing current of injury, which takes the form of a displacement of the P-Ta segment.*

*The constancy with which P-Ta segment changes in the dog and cat followed the production of auricular damage leads one to believe that possibly close examination of the comparable portion of the human electrocardiogram might be of value in those instances in which the rare clinical condition of auricular infarction with rupture is suspected. Although a number of such cases have been reported,² in only two were electrocardiographic records included; these, however, showed no definite changes.

This negative variation of the current of injury is present during the entire period of auricular activity, i.e., during invasion, balanced activity, and retreat, and, if of sufficient magnitude, it may affect the contour of the P-wave as well as the P-Ta segment and the Ta-wave. Moreover, the point at which the displaced P-Ta segment returns to the isoelectric line will serve to indicate the termination of the period of auricular activity, and thus the relative position of the normally invisible Ta-wave.

In this connection it is of interest again to call attention to the finding that the combined duration of the P-wave and displaced P-Ta interval, measured after cauterization and complete heart-block had been produced, was much greater than the normal P-R interval (Table I). In other words, it would appear from this that the electrical disturbances related to the terminal portion of the recovery period in the auricles are present but ordinarily obscured when the much greater changes due to the onset of ventricular activity are recorded. Only when the effects of the latter are eliminated, as by the production of complete heart-block, can the full extent of auricular activity be readily visualized by means of traumatizing the auricles. These observations are in accord with those of Brown,⁶ who utilized esophageal leads to obtain his data. It was his opinion that records obtained by esophageal leads are akin to electrograms and therefore give more accurate data as to the onset and duration of activity in the auricles than do the standard electrocardiograms. With this method he found that the Ta-waves in the esophageal curves extend well into the period in which the QRST waves are written and frequently exert some influence on the RS-T segment.

As has been stated before, examination of the electrocardiographic records of experimental premature auricular contractions reveals that stimulation of the right auricle produced upright aberrant P-waves in Lead I, whereas stimulation of the left yielded negative deflections. This is understandable if we compare the two auricles to a single hollow tube of muscle lying across the chest, grossly parallel to the lead line of Lead I, and being excited at one or the other end. In those instances, then, in which the impulse arises in the right auricle, either in its normal site, the sino-auricular node, or in some ectopic focus, its predominant direction of spread would be across the auricles from right to left, and thus a positive deflection would be recorded in the conventional Lead I. The reverse, of course, would hold for premature auricular impulses arising in the left auricle, and consequently negative deflections would be obtained. As expected under these conditions, the level at which the excitation wave originated (i.e., with respect to the upper or lower portions of the auricles), in the dog at least, did not significantly influence the contour of the ectopic P-wave in Lead I.

Comparable conclusions to the above could not be drawn for Leads II and III since the type of curve was generally the same in both leads (upright aberrant P-waves) no matter in which auricle, or on which surface, the ectopic focus was situated.

As in the case of analogous curves in the ventricles, the direction of the aberrant P-wave bears an inverse relation to the direction of the displaced P-Ta segment, when the site which was previously stimulated is then cauterized. Thus, as has been stated before, in right auricular stimulation, aberrant P-waves were obtained which were upright in Lead I and inverted in Leads II and III, while cauterization of the area from which the ectopic impulses arose resulted in P-Ta plateaus which were depressed in Lead I and elevated in the other two. The explanation which has been applied to similar phenomena in the ventricles⁴ can equally well be utilized for the changes in the auricles; for in brief it depends upon the fact that both excitation and injury of tissue develop relative negativity at the site of application and are thus in the same phase. Since the P-Ta displacement represents the negative variation of the current of injury (i.e., is opposite in sign to the latter) it must also be inverse in direction to the aberrant P-waves obtained by previously stimulating the region.

SUMMARY

The electrocardiographic changes following artificial stimulation and cauterization of the auricles were studied in a series of six cats and five dogs.

It was found that on cauterization of the auricular wall, a displacement in the position of the normally isoelectric line present between the P and R-waves, was consistently produced. This portion of the electrocardiogram, designated as the P-Ta segment, became elevated in Lead I when the left auricle was the site of injury and depressed in this lead on cauterization of the right auricle. In Leads II and III, the P-Ta segment assumed a depressed position regardless of which auricle was traumatized. The changes in the position of the P-Ta segment were considered to represent the negative variation of the auricular current of injury and the type of alteration was compared with that observed in the R-T transition following damage to ventricular muscle.

It was found that the P-Ta segment change produced by auricular trauma did not end with the onset of the R-wave, but instead extended for some time into the period of ventricular activity. This observation confirmed the view, held by other investigators, that under normal conditions the terminal portion of the recovery period of auricular activity is not ordinarily visible in the electrocardiogram since it occurs during the period in which the ventricular complexes are inscribed.

Upon artificial stimulation of the auricles, it was found that the direction of the aberrant P-wave in Lead I generally depended upon the lo-

cation of the site of origin as to one or the other auricle; being positive for instances of right auricular excitation and negative for left. In Leads II and III, the aberrant P-wave was positively directed for all sites on both auricles.

When the results of stimulation and cauterization of the same site were compared, it was observed that the direction of the aberrant P-wave had an inverse relationship to the direction of the displaced P-Ta segment (obtained with normal sinus rhythm).

We wish to express our gratitude to Mr. Joseph Marrus for his technical assistance in carrying out the preliminary experiments.

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CONGENITAL TRANSPOSITION OF THE GREAT ARTERIAL TRUNKS*

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THE publication of records of unusual congenital cardiac defects is of value in augmenting the literature available to workers who are particularly interested in this phase of heart disease. Congenital heart disease should be of more than academic interest. Recognition of the presence of these abnormalities in the living patient is of great practical value, and can be achieved only by constant clinical alertness and by the correlation of information obtained at post-mortem examination with physical signs and symptoms.

Transposition or incomplete torsion of the great arterial trunks consists of an alteration of the relations of the vascular trunks to each other and to the ventricles from which they normally arise; it is the result of a failure of normal rotation to occur during the early stages of cardiac development. Simultaneous with formation of the septum and with division of the heart into its chambers, there is a division and torsion of the common arterial trunk. The result of incomplete torsion is congenital transposition of the arterial trunks. Normally, the rotation proceeds clockwise and eventually describes an angle of 180 degrees, which is the mechanism that determines the relative positions of the pulmonary artery and aorta in the fully developed normal human heart; that is, the pulmonary artery arises from the right ventricle and anterior to the aorta. It is evident that if the process of torsion is impeded in its course or is not completed, any combination of positions of the pulmonary artery and aorta may result.

Rokitansky¹ recognized and described three types of transposition and his classification was used until Spitzer's observations² were published and his classification was adopted. In Rokitansky's classification, dextroposition of the aorta was considered as an entity apart from the group of anomalies classified under transposition, but Spitzer classified dextroposition of the aorta as Type I *Reitende Aorta*. This anomaly consists of an aorta that occupies a straddling position over a septal defect and receives blood from both ventricles. Type II of the classification of Spitzer corresponds to partial transposition as classified by Rokitansky in which both vessels, the aorta and pulmonary artery, arise from either ventricle, and is associated with a septal

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defect. The vessels may be stenosed or dilated but rarely are they of normal caliber. If this anomaly is accompanied by a pulmonary artery of normal caliber, it constitutes another anatomical complex, intermediate between Fallot's tetralogy and Eisenmenger's complex; the former is associated with a stenosed pulmonary artery and the latter with a dilated pulmonary artery.

Type III of Spitzer's classification includes cases in which no degree of torsion has occurred, and represents complete transposition in the classification of Rokitansky. In this type, the arteries have a relation-

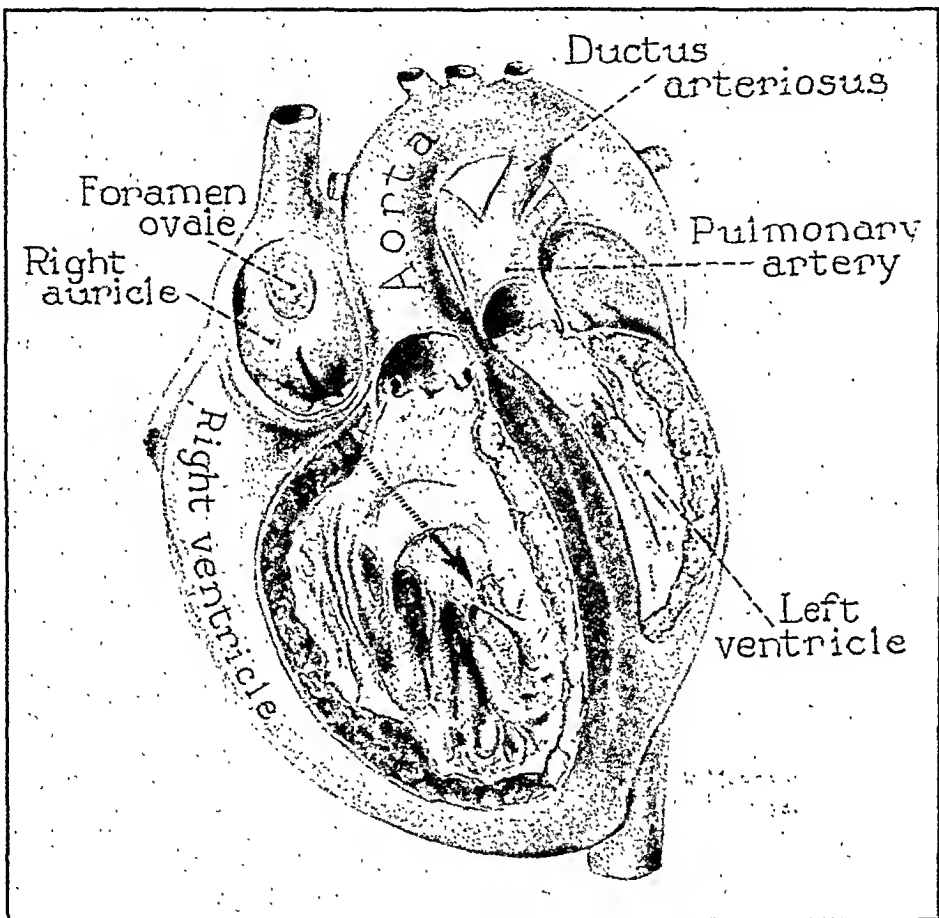


Fig. 1.—Diagram of the heart in Case 1. Complete transposition of the great vessels.

ship that is opposite to that of the normal one; that is, the pulmonary artery arises from the left ventricle and the aorta originates from the right ventricle. In these cases there may or may not be an associated interventricular septal defect.

Spitzer described Type IV as an anomaly comprising the complete defect of the interventricular septum in the cor biatriatum triloculare.

INCIDENCE

Of the 1,000 cases reviewed by Abbott³ there were recorded 69 cases of transposition in which this lesion was uncomplicated. Fifty-three of these 69 cases were classified as complete and 16 as partial trans-

position. Abbott stated in her 1932 monograph that there occurred only ten instances of partial transposition in which both vessels were of normal caliber.

Of the 87 major cardiac anomalies observed at The Mayo Clinic, there were five instances of transposition of the great arterial trunks.

REPORT OF CASES

CASE 1.—A white girl was born twenty days before admission. No evidence of attacks of cyanosis nor convulsions was given in the history. Forceful vomiting had occurred occasionally. The day before admission the infant had become fretful, nursed poorly, and the stools were of a loose consistency. Dyspnea and cyanosis developed and increased rapidly in severity. Examination revealed a child acutely ill, cyanotic, and gasping for breath. No physical findings referable to the heart were recorded. Oxygen was administered with no apparent improvement of her condition and the child died thirteen and a half hours after admission.

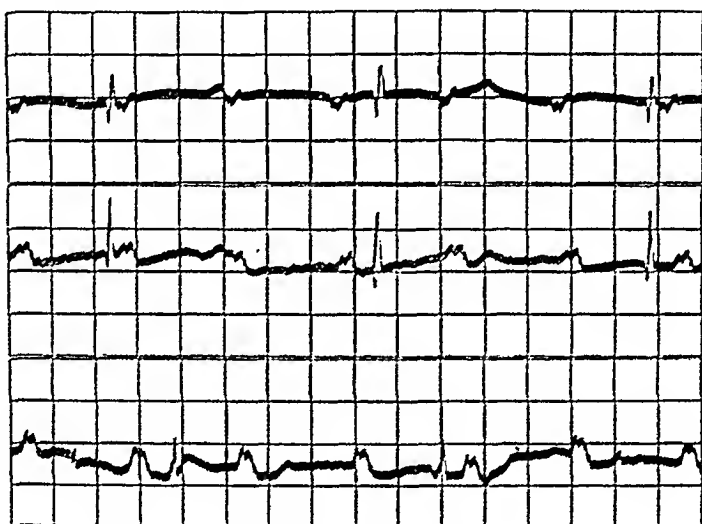


Fig. 2.—(Case 2). Electrocardiogram. Complete auriculoventricular dissociation.

At necropsy the heart was examined and weighed 50 gm. Externally no gross abnormalities were observed except that the right ventricle was more prominent than usual. The aorta originated from the right ventricle. This vessel was identified by the origins of the coronary arteries which were normal. The ductus arteriosus was patent and its lumen measured 2 mm. The pulmonary artery originated from the left ventricle and pursued its usual course. The venous structures were normal. The thickness of the right ventricular wall was 0.5 cm.; that of the left ventricular wall was 0.8 cm. The interventricular septum was intact and the foramen ovale was closed by a thin membranous flap. The aorta was to the right and in front of the pulmonary artery (Fig. 1).

CASE 2.—A white boy who had been delivered at full term was admitted for examination. His delivery was normal and his birth weight was 7 pounds and 3 ounces (3.3 kg.). Examination at birth revealed fair color, absence of the left external auditory canal and a rudimentary left ear; there was a dermoid at the temporal limbus of the left eye, the face was drawn to the right side and a cyst derived from the left branchial cleft was present. A systolic murmur, which became more pronounced shortly before death, was heard over the base of the heart; the

pulse was irregular and the rate was sixty beats per minute. The electrocardiogram indicated the presence of complete auriculoventricular dissociation (Fig. 2). Roentgenographic studies indicated that the stomach was in the right side of the abdominal cavity (*situs inversus*). Also a widening of the upper mediastinal shadow toward the right side of the thorax probably represented the thymus gland. The child failed to gain and marked cyanosis developed. On the eighteenth day after birth breathing became shallow and rapid, the cyanosis deepened, and the child died.

At necropsy the heart was found to occupy a normal position but the aorta curved downward on the right side. The heart was globular in shape, apparently equally divided into right and left ventricle. The endocardium appeared normal. The pulmonary veins entered the right auricle which appeared normal. The right auricle communicated with the right ventricle through a normal tricuspid valve. The foramen ovale was partly closed by a fenestrated membrane. The ductus arteriosus was patent; its lumen measured 3 mm. in diameter. The venae cavae entered the left auricle which communicated with the left ventricle by a normal mitral valve. The left ventricle gave origin to the pulmonary artery which had a bicuspid valve. The systemic aorta originated from the right ventricle and had normal valves and coronary origins. The aorta occupied a position to the right of, and anterior to, the descending aorta. There was an interventricular septal defect which measured 3 mm. in diameter.

CASE 3.—A normal boy, born at full term three months before, was brought for examination. His delivery had been spontaneous and his weight at birth had been 8 pounds (3.6 kg.); he had been cyanotic since birth. He had nursed well and had gained weight until one week before his admission to the hospital. At the time of his admission he was acutely ill, with cyanosis of the lips and fingers. Respiration was rapid and shallow and a systolic murmur was audible over the base of the heart, with its maximal intensity over the sternum. Scattered râles were heard over the entire thorax. Roentgenologic examination gave evidence of enlargement of the heart. The child was placed in an oxygen tent. His condition temporarily improved, then became progressively worse and he died six days after admission.

At necropsy the heart weighed 61 gm. and was brownish pink in color. There was no increase in epicardial fat. The right auricle appeared slightly dilated. The tricuspid valve appeared normal. The aorta was identified by the origin of the coronary arteries which arose in a normal manner. The aorta issued from the right ventricle and its orifice was normal. The pulmonary artery arose from the left ventricle and communicated with the aortic arch by a patent ductus arteriosus. The foramen ovale was open and the interventricular septum was intact. The vena cava and pulmonary veins were in normal relationship to the auricles. The pulmonary artery was to the right of, and anterior to, the aorta.

CASE 4.—A white boy, one month of age, whose birth had been normal, was admitted to the clinic. Cyanosis had not been noticed until three days after birth. Respiratory difficulty had developed at that time and roentgen therapy had been instituted on the basis of the diagnosis of an enlarged thymus. At the age of ten days, enlargement of the heart had been apparent and a murmur had been heard. Examination at the time of admission revealed an acutely ill child gasping for breath and markedly cyanotic. A systolic murmur was heard over the apex of the heart and râles were heard over the bases of both lungs posteriorly. An electrocardiogram gave evidence of marked right ventricular preponderance, and the P-waves were exaggerated in Lead II. The patient gradually failed in health, and death occurred two days after admission.

At necropsy the heart weighed 70 gm. and its color was brownish red; there was no excess epicardial fat. The ventricles appeared to be equal in size. The

right auricle received the venae cavae in a normal manner and communicated with the right ventricle through a normal tricuspid valve. The aorta arose from the right ventricle and its orifice was guarded by three normal semilunar cusps. The coronary arteries arose behind these cusps, one from the left sinus of Valsalva, and one from the posterior sinus. The pulmonary artery arose from the left ventricle and communicated with the aorta by a patent ductus arteriosus. The cusps of the pulmonary artery were normal in position and structure. The foramen ovale admitted a probe. The aorta was at the right of and anterior to the pulmonary artery. The interventricular septum was intact.

CASE 5.—A well-developed white boy, seven months of age, was admitted for examination. His birth had been normal, no difficulty in resuscitation had occurred, and there had been no cyanosis. He had progressed well for two months and then had begun to have vomiting spells accompanied by cyanosis. Roentgen therapy



Fig. 3.—(Case 5). Both aorta and pulmonary artery arising from the right ventricle; both vessels are of normal caliber.

applied over the thymus did not improve his condition. Roentgenological studies at that time revealed the stomach to be on the right side of the abdominal cavity. Response to treatment for pyloric obstruction was poor and the patient was removed to a hospital. At the time of admission the child was poorly nourished, mentally alert, but with dusky skin. A systolic murmur was heard over the base of the heart and the murmur was not transmitted. While the patient was in the hospital, otitis media and bronchopneumonia supervened and he died three weeks after admission.

At necropsy the heart occupied its normal position in the thoracic cavity, weighed 100 gm., and was reddish brown. It was globular in shape and appeared to have a large right ventricle and a small left ventricle. The consistency of the muscle was normal. There was no streaking in the muscle layer and the appendages, endocardium, and valves were normal. The inferior and superior venae cavae originated in the right auricle, in their normal positions. The coronary sinus was also in normal position. The foramen ovale was closed except for a slit-like patency

which was well guarded by a thick membranous flap. The cavity of the right ventricle was approximately five times the size of the left. The tricuspid valve measured 5.5 cm. and was normal in its relationships. The wall of the right ventricle measured 1 cm. in thickness while that of the left measured 0.75 cm. Both the pulmonary artery and the aorta were of normal caliber and arose in the right ventricle (Fig. 3). The aorta was identified by the origins of the coronary arteries which were in normal position. The aorta was situated to the right of and dorsal to the pulmonary artery. The ductus arteriosus was represented by a mere fibrous cord and there was a dimpling of the intima of both the aorta and pulmonary artery over the respective points of junction with the ductus arteriosus. The left auricle received the pulmonary veins and communicated with the small left ventricle through the mitral orifice which was guarded by a competent bicuspid valve which measured 3 cm. There was no point of exit from the left ventricle except by way of a patent interventricular septum; this opening measured 1 cm. in diameter and represented complete absence of the membranous septum (Fig. 4). The valves of



Fig. 4.—(Case 5). The same heart as that represented in Fig. 3 viewed from the left ventricle. A probe extends through the interventricular septal defect.

the aorta and the pulmonary artery were normal and there was no stenosis nor dilatation of either vessel. A blood vessel which measured 3 mm. in diameter originated from the posterior surface of the arch of the aorta. The destination of this blood vessel could not be determined. The blood vessel may have represented the remnants of the fourth left aortic arch.

This case represents Type II of Spitzer's classification or a partial transposition according to the older nomenclature of Rokitsansky.

DIAGNOSIS

The anomaly with which this paper is concerned is one of the group of anomalies associated with cyanosis and has no characteristic physical signs nor symptoms; however, the presence of situs inversus and cyanosis in a child should make one suspect that a congenital cardiac

anomaly exists, particularly transposition. Various murmurs associated with this anomaly have been described but none is pathognomonic. The murmurs probably originate from the defective septum which is usually present, rather than because congenital transposition exists. In approximately a third of the cases in which a stenosis of the pulmonic valve is a feature, a systolic murmur is heard over the second and third left intercostal spaces near the sternum. This murmur may be transmitted toward the left shoulder and is accompanied by a thrill. The murmur is often confused with that associated with a patent ductus arteriosus but the presence of cyanosis is a condition that favors making a diagnosis of stenosis of the pulmonic orifice. The electrocardiogram indicates the presence of right ventricular preponderance but again this is not characteristic of congenital transposition.

PROGNOSIS

The patients afflicted in the manner described here seldom live beyond childhood although rarely they have lived to middle age. The presence of an interventricular septal defect is associated with a slight increase of the life span, and is therefore an asset to these patients. The majority of patients, however, die within a few days or weeks after birth.

SUMMARY

In this study, five cases of transposition of the arterial trunks are presented (Table I). There are four cases of complete transposition according to the older classification of Rokitansky, and one case of partial transposition of the arterial trunks. Thus, according to Spit-

TABLE I
SUMMARY OF CASES

CASE	AGE AT DEATH	SEX	LESION	DUCTUS ARTERIOSUS	FORAMEN OVALE	INTERVENTRICULAR SEPTUM	MURMURS	ASSOCIATED ANOMALIES
1	20 days	Female	Complete transposition	Patent	Closed	Closed	None	None
2	18 days	Male	Complete transposition	Patent	Patent	Patent	Systolic	Situs inversus
3	3 months and 6 days	Male	Complete transposition	Patent	Patent	Closed	Basal systolic	None
4	1 month and 2 days	Male	Complete transposition	Patent	Patent	Closed	Apical systolic	None
5	7 months and 3 weeks	Male	Partial transposition	Closed	Patent	Patent	Basal systolic	Situs inversus

zer's more recent classification there are four cases of group III, representing a lack of torsion of the arterial trunks, and one case of group II, representing partial torsion.

The youngest patient was eighteen days of age and the oldest lived for seven months. In four of the five cases, the ductus arteriosus was patent but in one case it was represented by a mere fibrous cord and there was dimpling of the intimal surface of the pulmonary artery and aorta over the respective points of junction with the ductus arteriosus. In one case the foramen ovale was closed by a thin membrane, and it was but a slitlike opening in another case.

The interventricular septum was intact in three of the five cases and patent in two of them. The patency was attributable to an absence of the membranous portion of the septum. Systolic murmurs were audible in four of the five cases, but the patency of the fetal passages might well account for these murmurs. In two cases there was associated situs inversus. In four of the five cases the diagnosis of congenital heart disease was made without qualification before the patient died. The electrocardiogram indicated the presence of auriculoventricular dissociation in one case in which an interventricular septal defect existed.

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Department of Clinical Reports

LEFT AXIS DEVIATION IN DROPPED HEART*

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IT IS generally stated in the literature that the effect of habitus upon the electrocardiogram is such that a hypersthenic build tends to produce left axis deviation, whereas an asthenic build shows a tendency toward right axis deviation.^{1, 2, 3} However, cardiac disease may so modify the electrocardiogram that the effect of habitus is overcome. We have recently seen two asthenic patients who presented no evidence of heart disease but in whom the electrocardiogram displayed definite left axis deviation. Our inability to find similar cases in the literature has prompted us to report this finding.

Both patients were young adults, one a female thirty years of age, and the other a male of twenty-five, who had essentially the same symptoms. They complained of palpitation, ease of fatigue, and anorexia. The present and past histories disclosed nothing etiologically significant in heart disease. The physical examination in both instances was entirely normal. Both patients were of the asthenic habitus. There were no abnormal cardiac findings on physical examination. Fluoroscopic examination of the chest revealed a markedly dropped type of heart. Electrocardiograms were taken as part of the routine examination (Fig. 1). A diagnosis of neurasthenia was made in both instances.

DISCUSSION

Left axis deviation is usually due to one of two factors, cardiac displacement or left ventricular hypertrophy. Elevation of the left leaf of the diaphragm, whether due to habitus, disease, respiration, or any increase of intra-abdominal pressure, may produce counter-clockwise displacement of the heart with a tendency toward left axis deviation. Clockwise displacement has the opposite effect.¹ In our patients ptosis of the heart would be expected to produce the latter effect. This was not borne out by the electrocardiograms (Fig. 1). It is well known that any disease which will produce hypertrophy of the left ventricle and disturb the normal relationship between the muscle masses of the left and right ventricles will tend to produce left axis deviation. Such a factor could more than neutralize a tend-

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ency toward right axis deviation produced by ptosis. Our patients showed no evidence of left ventricular hypertrophy nor any etiological factor known to produce left ventricular strain. Since the above factors cannot explain the left axis deviation, an interpretation must be sought elsewhere.

There is adequate experimental evidence to indicate that at least two other factors may influence axis deviation. These are lateral shift of the entire heart and rotation of the heart on its longitudinal axis. Kountz and associates⁴ have shown in revived human hearts that shifting of the heart to the right gave a left axis deviation, and shifting to the left, a right axis deviation. Fluoroscopic examination of both of our patients failed to reveal any evidence of lateral displacement of the heart.

If one views the teleoroentgenograms of an asthenic and a hypersthenic patient, it is clearly seen that the total muscle mass of the

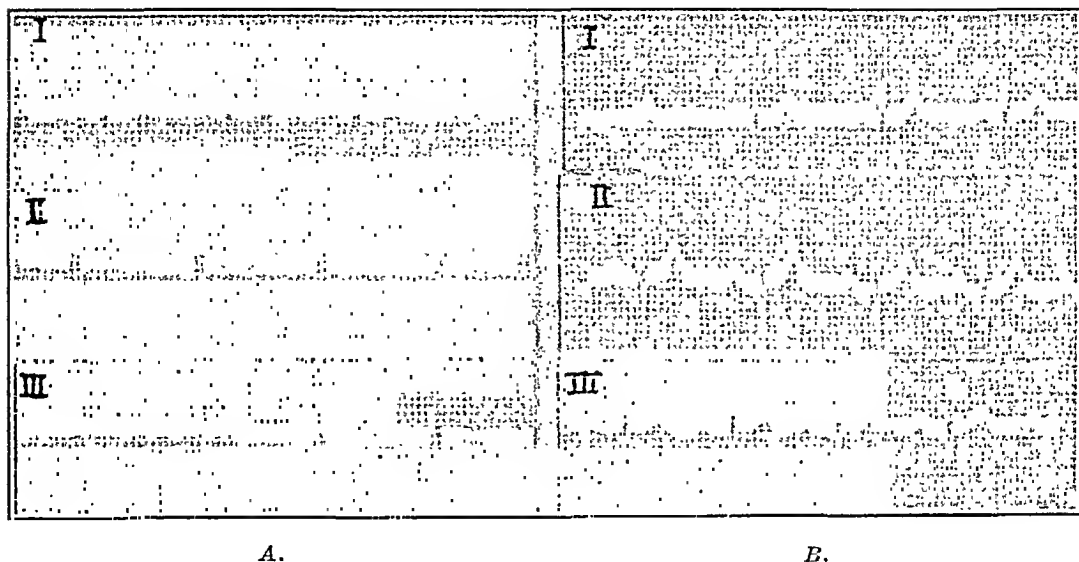


Fig. 1.—Electrocardiogram illustrating left axis deviation in a normal female (A) and male (B) of asthenic habitus with cardiac ptosis.

asthenic heart is farther to the right even though the right border is not displaced to the right. The muscle mass is also more caudad. Such displacement appears to be about a fixed point as a fulcrum at or near the base of the heart. If this fulcrum were fixed, the motion would be about a fixed point and the remarks already stated concerning clockwise and counterclockwise motion would hold. However, if the fulcrum were movable, at least to some extent, an effect of lateral shift of the entire heart might come into play. Obviously, in patients the predominant motion is of the former type. If it were in some instances of the latter type, an explanation of left axis deviation would be evident. We have no evidence to confirm or deny such a mechanism in our patients.

Ackerman and Katz⁵ demonstrated a complete reversal of QRS in Leads I or III when the heart of the dog was rotated on its own longi-

tudinal axis. With the right ventricle anterior, left axis deviation was found; with the left ventricle anterior, right axis deviation. Such changes occurred with rotation as little as 50° . Motion of this type cannot be observed in the intact individual. It is hardly conceivable that the hearts of the asthenic and hypersthenic individuals differ only by position in one plane, or that the hearts of all asthenic or hypersthenic individuals rest upon the same longitudinal axis. Upon these bases, Nathanson⁶ explained the inconsistency in the change in electrical axis with change in position of the body. One can readily see that right or left axis deviation may theoretically occur in patients with dropped hearts, depending upon the summation of the above factors.

SUMMARY

The occurrence of left axis deviation in a patient with dropped heart does not necessarily mean cardiac hypertrophy. The known effects of change in cardiac position upon the electrocardiogram can adequately explain such a finding.

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DEXTROCARDIA WITH SITUS INVERSUS COMPLICATED BY HYPERTENSIVE AND CORONARY HEART DISEASE

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DEXTROCARDIA with or without situs inversus is an uncommon but not a rare condition. Its association with hypertensive and coronary heart disease is, however, so unusual, particularly in its effect on the electrocardiogram, that we are presenting a case herewith:

A number of historical reviews have been published on the subject of dextrocardia itself. Of historical interest is the fact that Aristotle¹ observed transposition of viscera in animals. Fabricius³ (1606) and Severinus⁸ (1643) were apparently the first to describe dextrocardia in the human. Marie de Medici was one of two cases with this congenital anomaly reported by Riolanus⁶ in the seventeenth century. Senac⁷ (1749) was the first to classify dextrocardia into the acquired and the congenital types.

Since the early part of the nineteenth century important contributions have been made to the clinical recognition of isolated dextrocardia and dextrocardia with situs inversus (Küchenmeister,⁴ 1824, and Bouillaud,² 1835). The first to employ roentgenography for the recognition of this condition was Velssemyer⁹ (1897). Waller¹⁰ (1889), who was the first to obtain a tracing of the action current of the human heart by means of the capillary electrometer, was also the first to obtain such tracings in two cases of dextrocardia with situs inversus. He showed that in such cases the usual Lead I is inverted and Leads II and III are transposed. This finding, in the absence of complicating heart disease, has been repeatedly confirmed since.

The clinical incidence of dextrocardia, presumably with situs inversus, was pointed out by Le Wald to be one in thirty-five thousand physical examinations of recruits for the United States Army. Still more infrequent is the association of dextrocardia with acquired functional or organic defects of the cardiovascular system. Willius¹¹ recently described dextrocardia with situs inversus and hypertension. The purpose of the present report is to record the hitherto undescribed association of dextrocardia with situs inversus, hypertension, and coronary disease.

CASE REPORT

C. H. W., a sixty-seven-year-old American unemployed chef, was first seen by us Sept. 26, 1937, because of a cold and a nonproductive cough of six days' duration. In 1927 he had had a nosebleed and at that time he was first told that he had high blood pressure; he has been treated for the hypertension ever since. He had passed

an insurance examination in 1922. In 1934 he began to have dyspnea on walking up one flight of stairs. In June, 1935, while working as a chef he lost consciousness for an undetermined length of time. On regaining consciousness, he had no paralysis. He was able to dress and go home unassisted. For several weeks following this experience, he was treated in bed for a "blood clot on the brain." He has had no recurring syncope attacks. He began to suffer from sharp, penetrating pain over the left breast on effort or excitement soon after his syncope attack in 1935. The pain is severe, lasts a few minutes, does not radiate, and is relieved quickly by nitroglycerine, grain 1/100. There has been no edema of the ankles or recent weight loss. His present weight is 168 pounds and his best weight has been 197 pounds. He has lost 30 pounds in two and a half years, without dieting. He uses tea, coffee, and tobacco in moderation, but no alcohol.



Fig. 1.—Teleroentgenogram demonstrating congenital dextrocardia with situs inversus, cardiac enlargement of the left ventricular type and increased density of the aorta, the knob of which is seen at the right of the upper sternum. The lung markings are increased. Note the gas below the diaphragm on the right and the high position of the left leaf of the diaphragm.

He has had mumps, pertussis, malaria in 1907, pleurisy in 1934, erysipelas in 1936, and pneumonia twice in 1936. There have been no operations or injuries. He was left handed in youth.

Family History.—Father died at fifty-two years, and mother at sixty-four years; the causes of their deaths are unknown. One brother was buried in a mine disaster. There is no history of consanguineous marriage.

Physical Examination.—The patient was a moderately well-developed and well-nourished sixty-seven-year-old white male, nervous, and not acutely ill. His temperature was 98.6° F. His pulse was regular at a rate of 72. The respiratory rate was 20. His blood pressure was 270 systolic and 130 diastolic. He weighed 168 pounds dressed.

Except for dental caries and an increased carotid pulsation, the examination of the head and neck showed nothing abnormal.

The chest was emphysematous, and tactile fremitus and pulmonary resonance were unimpaired over the lung fields. Below the right fifth rib anteriorly and over the right upper quadrant tympany was elicited; below the left fifth rib anteriorly and down the costal border dullness was present. The breath and voice sounds were normal; an occasional sibilant râle was heard anteriorly.

Heart.—The maximum apex impulse was found in the right fifth interspace in the anterior axillary line 11.5 cm. to the right of the midsternal line. The midclavicular

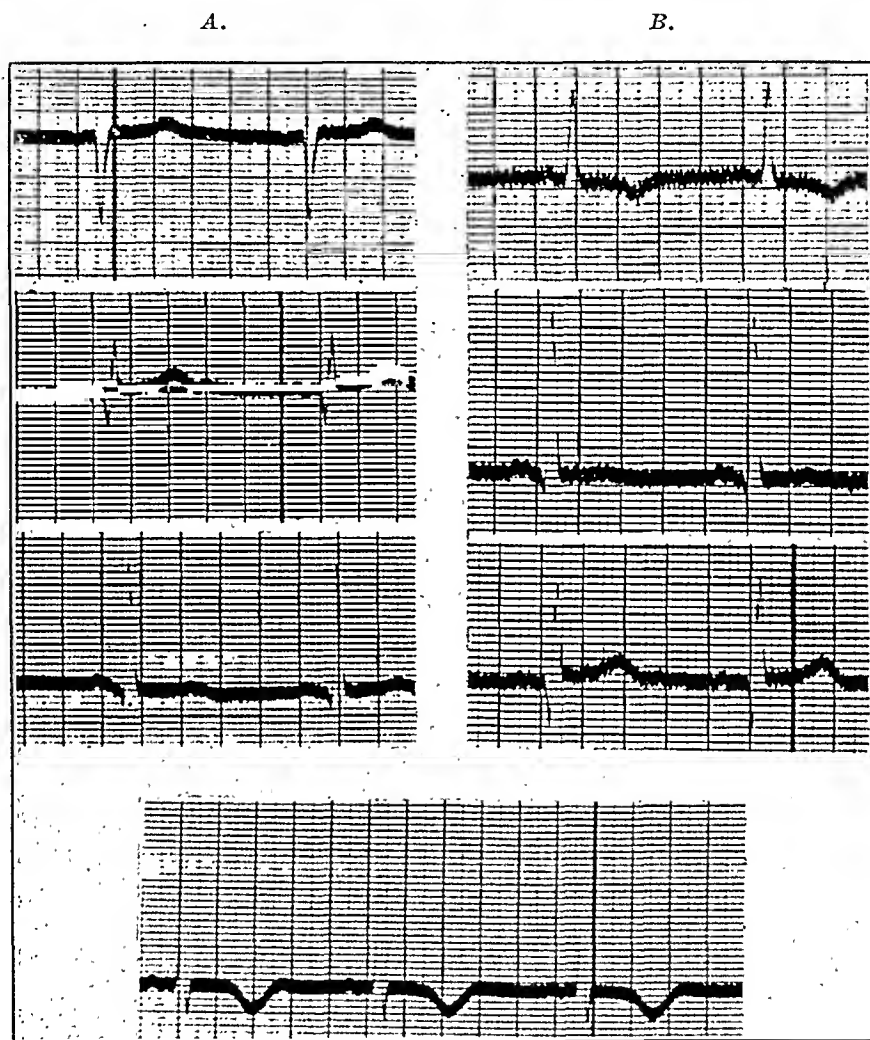


Fig. 2.—A. Electrocardiogram (Leads I, II, III, and IV*) showing normal rhythm, inverted P_i, marked right axis deviation (due to the combination of congenital dextrocardia and hypertensive heart disease), and changes due to coronary disease (upright T_i, prominent Q_s, high origin of T_s, low T_s, and inverted T_s). See text.

B. Electrocardiogram with Leads I, II, and III taken with a reversal of the arm wires—to “correct” for the dextrocardia.

Time interval equals 0.1 second, amplitude 1 mm. equals 0.1 millivolt.

*Lead IV taken according to the new method with exploring electrode at the cardiac apex, indifferent electrode on the right arm, and polarity so arranged that positivity is represented by upstrokes and negativity by downstrokes: the normal Lead IV has a diphasic QRS-wave with upright first phase (R) and an upright T.

line was 9 cm. to the right of the midsternum. The apex impulse was localized, forceful and regular. The left border of dullness was 4 cm. to the left of the midsternal line in the fourth interspace. There was no supracardiac dullness. There were no thrills. The heart sounds were distant over the left chest; over the right chest the heart sounds were loud at a regular rate of 72. The second sound in the

left second interspace* was greater than that in the right second interspace. A slight systolic murmur was heard at the apex. The pulses were full and equal. The blood pressure was 270 systolic, 130 diastolic, without alternation. Vigorous axillary and brachial pulsations were present.

The abdomen was flat; there was no tenderness or rigidity, and abdominal organs were not palpable. The right testicle was lower than the left.

Except for an irregular melanotic pigmentation and numerous varicosities, the extremities were normal.

The reflexes were active and equal.

Fluoroscopic Examination.—The heart was completely transposed, the mirror image of the usual position. The left border of the heart was blunt and rounded; the right border was sharp with a prominent apex visible in the right chest. The aorta was slightly increased in density and extended upward to the right. The retrocardiac space and aortic arch were visualized in the right anterior oblique view. The right leaf of the diaphragm was lower than the left; the stomach with its gas bubble was seen on the right; the liver was on the left. The lung fields and hilar shadows appeared normal; the diaphragmatic excursion was normal.

Teleroentgenographic Examination.—This was confirmatory of the fluoroscopic findings noted above (Fig. 1).

Electrocardiographic Examination.—Normal rhythm, ventricular rate 55. Inverted P-waves in Lead I, inverted QRS-waves in Lead I, marked right axis deviation, slight widening and notching of the QRS-waves in Leads II and III, prominent Q-waves in Lead II, upright T-waves in Lead I, high origin of the T-waves in Lead II, low T-waves in Lead III, late deep inversion of the T-waves in Lead IV (Fig. 2).

DISCUSSION

The recognition of dextrocardia with situs inversus in this case depended upon the physical examination, the visualization of the transposition of the heart, the stomach, and the liver by roentgen ray, and the inversion of the P-waves in Lead I of the electrocardiogram.

The presence of hypertensive heart disease was recognized by the elevated blood pressure and the enlargement of the heart on physical and x-ray examination, and was suggested by the unusually marked right axis deviation in the electrocardiogram in the presence of congenital dextrocardia.

The diagnosis of coronary heart disease was made upon the history of pain just to the left of the sternum caused by effort or excitement and relieved by nitroglycerin, and upon the unusual electrocardiogram.

The electrocardiogram is of particular interest and is apparently unique. In the uncomplicated case of congenital dextrocardia with the situs inversus the electrocardiogram shows merely total inversion of Lead I (P, QRS, and T) and transposition of Leads II and III. The unusual features of the present electrocardiogram are the marked amplitude of the inverted QRS in Lead I (due to the acquired heart disease superimposed on the dextrocardia), the upright T_1 , which is to be interpreted as a "coronary T," the prominent Q_2 and high origin of T_2 , which would ordinarily signify " Q_2T_2 coronary changes," the low T_3 having

*Actually the aortic area, because of the transposition.

the same significance as a low T_2 in the case of a heart normal in position, and a deeply inverted T_4 (Lead IV being taken in relation to the heart position exactly as in the normal person). The exact correlation of the electrocardiographic changes with damage or coronary insufficiency in any one or more areas in the heart muscle is difficult, as so often occurs in a chronic case. The changes in Leads I and II (the usual Lead III) suggest that both apical (or marginal) and basal areas are affected. The presence of R_4 tends to rule out the existence of a large apical scar.

SUMMARY

A case of a man, sixty-seven years old, is presented with congenital dextrocardia and situs inversus complicated by hypertensive and coronary heart disease. The electrocardiogram is of particular interest since it shows the effect of the various conditions cited. We have found no other such case recorded.

SUPPLEMENTARY NOTE.—Since the completion of our paper there has appeared an interesting case report by Crawford and Warren of a patient with congenital dextrocardia and situs inversus complicated by coronary thrombosis. The electrocardiogram, however, is quite different from ours for two reasons: In the first place, in their case the infarct was evidently situated at the base of the left ventricle with inversion of the T-waves in Leads II and III, and Lead I was normal; in the second place, there was no abnormal axis deviation after correction for the dextrocardia. Thus, both their case and ours are unique.

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AN UNUSUAL P-WAVE IN LEAD IV*

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RECENTLY, an unusual contour of the P-wave was encountered in Lead IV, which was considered to indicate a shift of the heart's position to the left with an approximation of the right auricle to the chest wall in the neighborhood of the precordial electrode in the fourth interspace to the left of the sternum. This interpretation was confirmed by the roentgenogram. It is felt that this peculiar P-wave is of sufficient interest to merit the reporting of the case in which it was found.

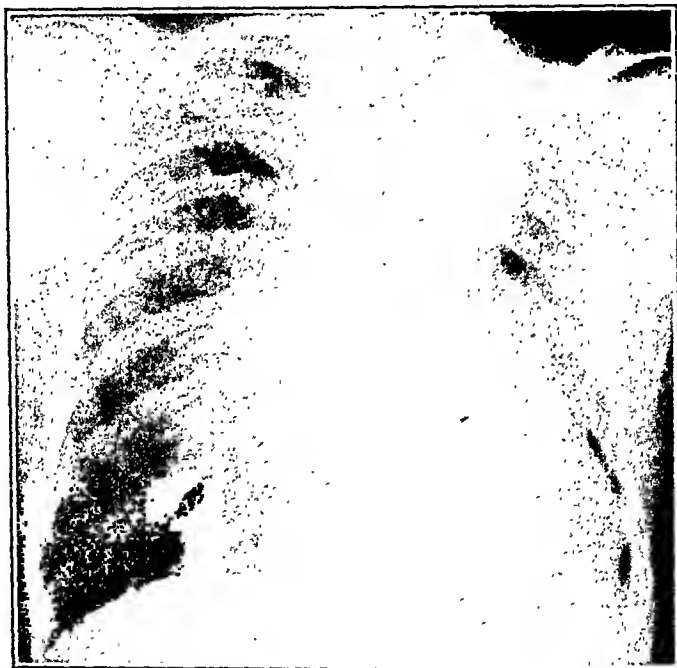


Fig. 1.

CASE REPORT

M. F., a colored male, aged sixty-five, was admitted on Dr. W. Buchbinder's service, complaining for two months of shortness of breath, cough and swelling of the ankles. The cough was productive and the patient was orthopneic. There was slight clubbing and cyanosis of the fingertips. The neck veins were distended and the patient was edematous. There was limitation of respiratory motion of the left upper chest with impairment of resonance in this area. There were coarse, moist râles at the base of both lungs. The heart was moderately enlarged to the left and the basal dullness was widened. A systolic murmur and a protodiastolic gallop were heard over the base of the heart. The blood pressure was 190/130 and the blood Wassermann reaction was negative.

*From the Cardiovascular Department, Michael Reese Hospital.

An x-ray plate was taken while the patient was in the hospital (Fig. 1) and showed a cardiothoracic ratio of 15.7/27.3. There was prominence of both the left ventricular and pulmonary bows. The aorta was of the short squat type. Calcified deposits were present in both axillae and cervical regions. The entire upper lung field from the second rib anteriorly up to the apex was densely clouded and contained large plaques of calcified deposits. On fluoroscopy, these plaques were found to be in the posterior half of the lung field. There was retraction of the trachea and superior mediastinum toward the lesion in the left upper lung field. This roentgenogram was interpreted as being indicative of old tuberculosis, with calcareous deposits in the left upper lung field and traction on the heart by this lesion. The heart itself was considered to be abnormal.

The clinical diagnosis was arteriosclerotic heart disease, hypertension with marked enlargement of the left ventricle, and congestive heart failure. After a short stay, the patient left the hospital improved in health.

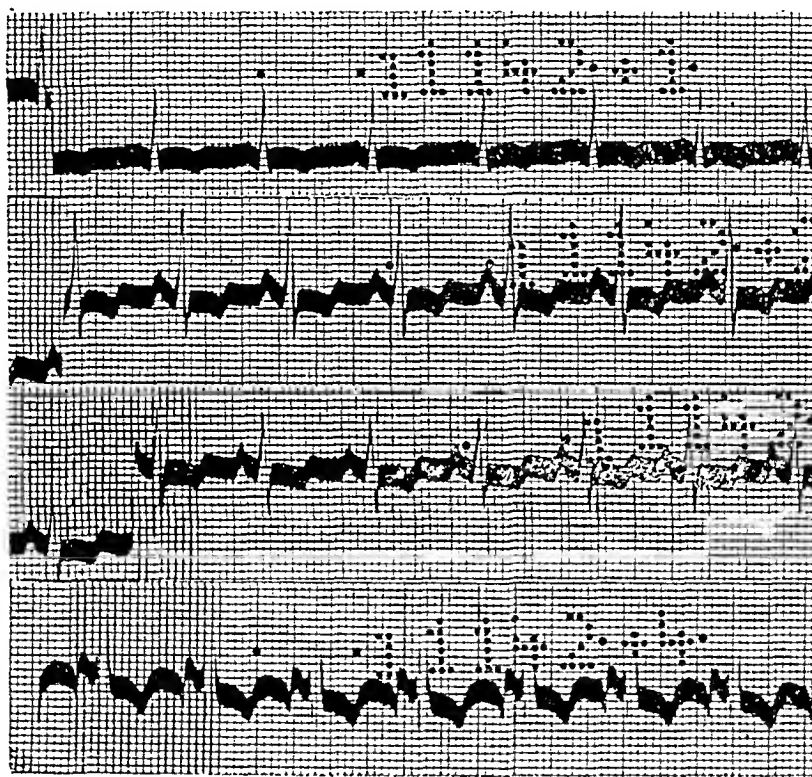


Fig. 2.

COMMENT

The electrocardiogram (Fig. 2) taken on Nov. 2, 1936, was interpreted as indicating an abnormal heart. On the basis of P_4 , and without knowledge of the other findings of the patient, this was interpreted as follows: The diphasic P_4 looks like a P-wave which is recorded over the auricle and hence would suggest that the heart is displaced to the left. The P-wave in Fig. 2 resembles the P-wave usually obtained when the precordial electrode is placed over the second or third interspace in the right parasternal line and also resembles in contour the type of wave reported by Wilson, Macleod, and Barker,¹ among others, when an electrode directly on the exposed auricle is paired with an indifferent electrode at a distance.

With the precordial electrode placed in the fourth interspace to the left of the sternum, a P-wave such as this has not been seen in any other of the more than 3,000 records taken at the Heart Station. It was considered that such a P-wave should therefore indicate that the auricle in this patient had been shifted so as to lie close to the region where the precordial electrode was located, hence it would follow that the heart had been displaced to the left. This surmise was verified by the roentgenogram, which showed that the heart had been pulled over toward the left. This case serves to emphasize the importance of the heart's position in determining the character of the electrocardiogram obtained with precordial electrodes.

SUMMARY

A case is presented showing an unusual P-wave in the fourth lead, when the precordial electrode is in the fourth interspace to the left of the sternum. This consisted of a diphasic P-wave with sharp transition between the two phases, resembling the type of wave seen when a unipolar lead is employed with one electrode directly over the auricle. In this case the abnormal P was associated with a displacement of the heart to the left caused by traction which resulted in placing the right auricle beneath the area of the precordial electrode.

I wish to acknowledge my indebtedness to Dr. Louis N. Katz, who first suggested the interpretation of the electrocardiogram, for his guidance in preparing this report.

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TWO-TO-ONE AND THREE-TO-ONE LEFT BUNDLE-BRANCH BLOCK IN THE PRESENCE OF AURICULAR FLUTTER

CASE REPORT*

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ELECTROCARDIOGRAMS revealing ventricular responses that alternately show bundle-branch block and normal intraventricular conduction in the presence of normal sinus rhythm and normal P-R intervals are distinctly rare. Reported instances include those of Leinbach and White¹ and Kelly.² Cases in which ventricular complexes of normal duration appear with varying frequency in the presence of bundle-branch block are somewhat more common.³⁻⁹ Robinson¹⁰ has reported an instance of alternating normal intraventricular conduction and bundle-branch block in the presence of complete heart-block, and White and Stevens¹¹ have recorded the appearance of transient bundle-branch block during a paroxysm of rapid auricular flutter. However, we have not encountered in the literature or in the electrocardiograms of over 11,000 patients on file at the Rhode Island Hospital, the combination presented by the case herein reported.

CASE REPORT

G. M., a sixty-five-year-old, unmarried salesman, was first seen by Dr. Alex M. Burgess on Aug. 12, 1936, complaining of recurrent lightheadedness and faintness.

A year and a half before, he had experienced some indefinite chest pain, at which time his physician told him he had a "heart attack" and kept him in bed for one week. Digitalis had been taken since, sporadically. While there had been mild shortness of breath on stairs, there had at no time been any edema, cough, or palpitation.

He stated that after lifting a heavy box nine days previously, he had felt suddenly weak and faint—a symptom occasionally noticed on exertion for the past year and a half. There was no pain or dyspnea with this attack. The family history and past history were noncontributory. Physical examination by Dr. Burgess included the following findings. The blood pressure was 152/84. The heart rate was 84 beats per minute, with an irregular rhythm. No murmurs were heard, and there was no apparent enlargement. The lungs were clear, and there was no edema. Moderate sclerosis of the retinal and peripheral arteries was present.

Eleven days after his first visit to Dr. Burgess, he became dizzy and noticed dimness of vision while climbing stairs after a hard day. He perspired freely, felt some oppression in his chest, and was apprehensive. The next morning his physician found the blood pressure to be 190/110. The heart rate was 90, and the rhythm still irregular. He was advised to enter the Rhode Island Hospital for further study.

He was admitted to the hospital on the same day, twelve days after he had first been seen, and appeared comfortable and lay flat in bed without distress. Examination revealed the same findings as before, except that the blood pressure had fallen to 150/82. There was no fever.

*From the Heart Station of the Rhode Island Hospital, Providence, R. I., under the direction of Dr. Frank T. Fulton.

Laboratory data, including a Wassermann test, blood count, urine examination, and blood chemistry, provided no significantly abnormal findings.

Orthofluoroscopy revealed a prominent aortic arch and clear lung fields. The total transverse diameter of the heart was 13.4 cm., and the internal thoracic diameter measured 23.4 cm.

The patient was fully digitalized and was discharged on Sept. 9, 1936, after an uneventful stay. Since then he has been active and generally well. There is still occasional faintness. He has continued to take one pill of digitalis (0.1 gm.) daily.

DISCUSSION

In Fig. 1, Lead I, it is apparent that the ventricular rate is perfectly regular, and that every second beat reveals left bundle-branch block (new terminology). In Lead II the same condition prevails except in

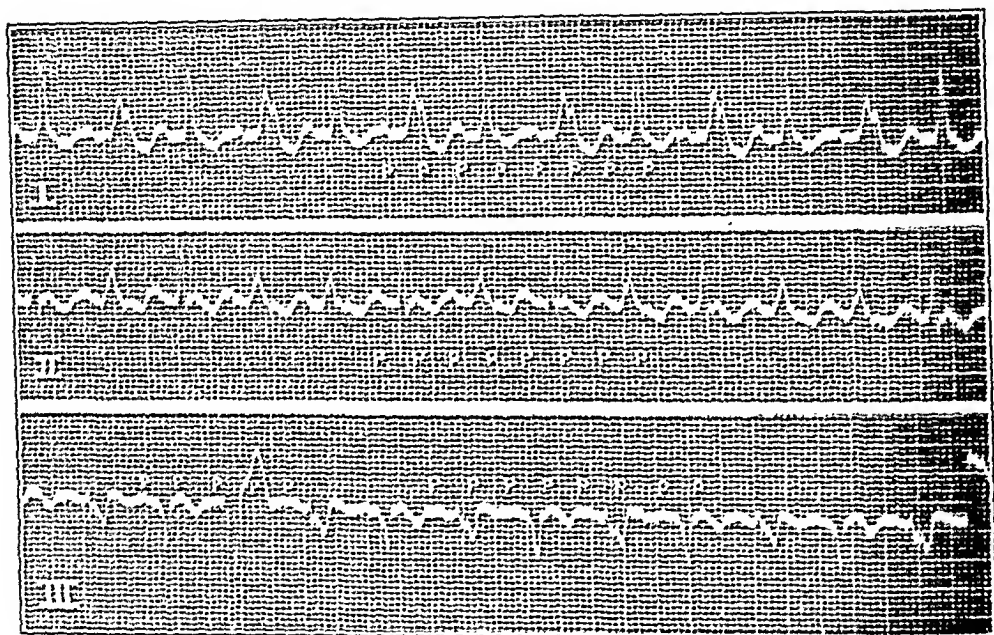


Fig. 1.—The three standard leads taken Aug. 14, 1936. The ventricular rate is 127, and the auricular rate 254 per minute (auricular flutter with 2:1 block). Through most of the tracing every second ventricular beat shows left bundle-branch block (2:1 and occasionally 3:1 left bundle-branch block). The normal ventricular response measures 0.08 sec.; the widened ventricular beats measure 0.14 sec. One ventricular extrasystole is present in Lead III.

two places, where two beats showing bundle-branch block occur in succession. In Lead III the rate is regular except for one ventricular extrasystole, and normal beats and those showing bundle-branch block alternate. Throughout the tracing the interval between ventricular beats approximates 0.46 sec. Between the ventricular extrasystole and the preceding beat, the interval is 0.41 sec., and between it and the following beat the interval is 0.52 sec. The early occurrence of this beat is evidence of its identity as a ventricular extrasystole rather than as an aberrant ventricular response from a normally conducted auricular impulse.

How long the unusual condition shown in Fig. 1 endured we do not know, as the next available tracing was taken eleven days later (Fig.

2A). At that time the ventricular rate had slowed, and the record presents the ordinary appearance of auricular flutter, with the ventricular rate controlled by digitalis. Following this, seven tracings were taken at intervals through Dec. 4, 1936. All of these were very similar to that shown in Fig. 2A. The flutter persisted with a constant auricular rate; the ventricular rate varying between 42 and 82 beats a minute. Bundle-branch block did not recur, and the QRS complex always measured between 0.08 and 0.09 sec. On Aug. 27, 1936, carotid sinus pressure was tried and increased the block to 8:1 but did not alter the appearance of the ventricular complex.

The final tracing, Fig. 2B, was taken fourteen months after that shown in Fig. 1. At this time normal sinus rhythm prevailed, with frequent ventricular extrasystoles. The normally conducted ventricular responses

A.

B.

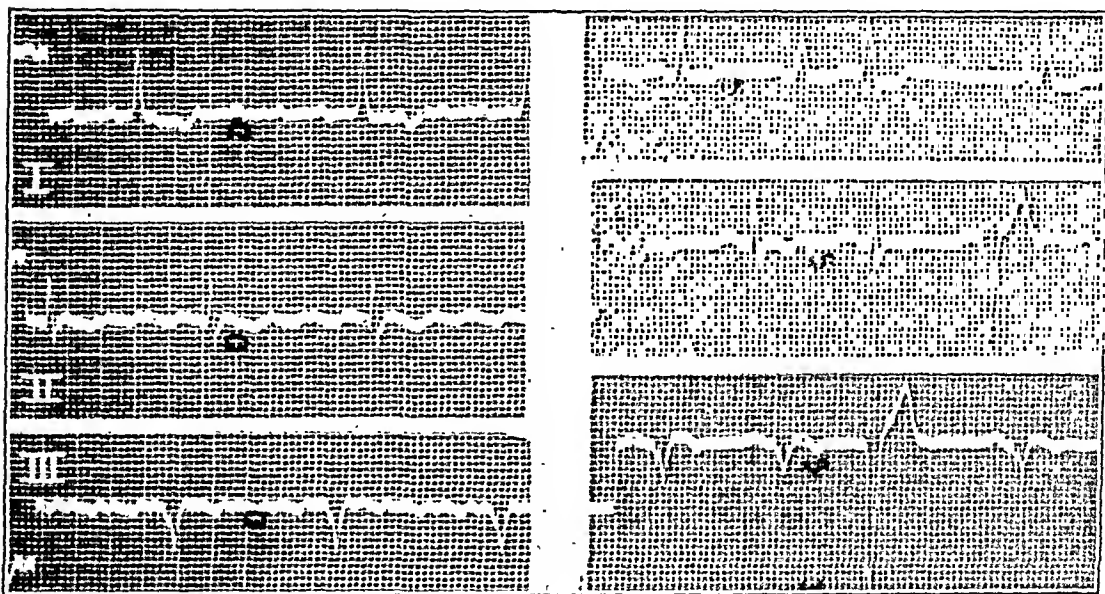


Fig. 2.—A, The three standard leads taken Aug. 25, 1936. Auricular flutter persists. The A-V block has been increased following digitalis administration to 4:1 and 6:1. The ventricular rate is 54 per minute. The bundle-branch block has disappeared, the QRS complexes measuring 0.08-0.09 sec.

B, The three standard leads taken Oct. 14, 1937. The auricular flutter has reverted to normal sinus rhythm with frequent ventricular extrasystoles. The conducted ventricular responses are slightly wider, measuring 0.08-0.10 sec. Bundle-branch block is absent.

show slight widening, but bundle-branch block is absent. A tracing in the fourth lead taken at this time, but not reproduced in Fig. 2B, revealed a large Q-wave and a normally inverted T-wave.

In the light of the clinical observations on our patient and the evidence contained in references cited at the beginning of this paper, we believe that the abnormality of ventricular beat shown in Fig. 1 resulted from the rapid ventricular rate in the presence of significant disease of the coronary arteries. It is possible that the conduction defect in the left bundle was associated with thrombosis of one or more of the small vessels supplying this area. We rather expect the bundle-branch block to recur eventually, but we have not observed its reappearance in fourteen months.

SUMMARY

A case is reported illustrating the unique combination of auricular flutter and 2:1 and 3:1 left bundle-branch block. Subsequent tracings covering a period of fourteen months are described, and the probable etiologic factors in the original electrocardiographic abnormality are suggested.

We wish to express our indebtedness to Dr. Alex M. Burgess, who took and made available to us the tracing reproduced in Fig. 1, and provided the original clinical observations on this patient.

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Department of Reviews and Abstracts

Selected Abstracts

Page, Irvine H., and Sweet, J. E.: The Effect of Hypophysectomy on Arterial Blood Pressure of Dogs With Experimental Hypertension. *Am. J. Physiol.* 120: 238, 1937.

Hypertension of the order of 240/160 mm. Hg was produced in dogs by constricting the renal arteries of dogs by means of Goldblatt's clamp. It was maintained for several months. Hypophysectomy in these animals reduced the arterial pressure to levels slightly above normal (150/100) or below normal (90/40) within a period of twenty days. Hypophysectomy in normal dogs reduced the arterial pressure only slightly (from about 140/170 to 116/50).

Increasing the constriction of the renal arteries after hypophysectomy again produced a rise in blood pressure, but this tended to be less marked and transient, especially in the dogs which became sluggish and fat and exhibited reduced basal metabolism and often diabetes insipidus. The rise was better maintained in dogs which were thin and active and with normal or elevated basal metabolism.

After hypertension had been reduced by hypophysectomy, feeding thyroid (0.8 gm.) raised the blood pressure moderately (190/120), and injection of theelin (1 c.c. daily) or antuitrin-S (1 c.c. daily) had no effect.

The effect of hypophysectomy on hypertensive dogs is believed to be an indirect one. It is postulated that the responsiveness of the blood vessels to chemical stimuli from the kidneys with constricted renal arteries is reduced. This may be due to lack of the secretions which may in turn be due to withdrawal by hypophysectomy of the chemical stimuli normally afforded them by the hypophysis.

AUTHOR.

Malméjac, J., and Desanti, E.: Concerning the Cardiovascular Properties of Hypophyseal Extract. *Compt. rend. Soc. de biol.* 125: 475, 1937.

Watery extract of the hypophysis (Carrion Co.) was injected intravenously into dogs anesthetized with chloralose and was found to give rise to a sharp fall in arterial pressure accompanied by dilatation of peripheral vessels (plethysmographic measurements) in kidney and foot. The surprising result was that the spleen, in contradistinction to the behavior of other organs, contracted sharply.

STEELE.

Scheiner, H.: Hypertensive Action of an Ultrafiltration Extract of Dog Spleen Previously Treated With Posterior Pituitary Extract. *Compt. rend. Soc. de biol.* 125: 125, 1937.

An extract of spleen, obtained from the fresh organ after a period of electrical stimulation of its nerve by ultrafiltration, has been previously studied by the author, and it was shown to cause usually a fall in arterial pressure, but in a certain number of instances (8 out of 22) was followed by a rise. He has also shown that

when the animal has been previously cocaineized and atropinized, injection of the spleen extract was regularly followed by a rise in arterial pressure. In the present series of experiments the extract of spleen was given to dogs under chloralose anesthesia after they had been treated with an extract of the posterior pituitary gland. Just as after cocaine and atropin the splenic extract now gave rise regularly to a rise in pressure. One important difference was noted; whereas injection of cocaine and atropin had to be repeated after an interval of one hour to maintain the pressor effect of the splenic extract, the effect of posterior pituitary extract lasted for at least four or five hours. Scheiner believes the extract of the hypophysis—it is soluble in 80 per cent and insoluble in 95 per cent alcohol and insoluble in acetone—to be similar to, if not identical with, vasopressin.

STEELE.

Dicker, E.: An Autolyzing Kidney Gives Rise to Substances Which Produce Hypertension. *Compt. rend. Soc. de biol.* 126: 88, 1937.

Both renal arteries of dogs were completely clamped. Twenty-four hours later the animals were anesthetized by chloralose, and arterial pressure in the femoral artery was recorded while releasing the clamps, first on the one, and then the other side. Arterial pressure rose 40 to 50 mm. Hg and remained elevated for about twenty minutes after release of each artery.

If instead of opening the clamps the kidney was perfused with Locke's solution and the perfusate injected into the *femoral* vein, a similar rise occurred. The rise in pressure failed to occur if the perfusate was injected into a *mesenteric* vein.

The vasopressor principles of the autolyzing kidney survive prolonged boiling, oxidation with potassium permanganate, and aging; they are soluble in alcohol but not in ether.

STEELE.

Bärttschi, W.: The Reaction of the Coronary Arteries to Histamin. *Arch. f. d. ges. Physiol.* 238: 606, 1937.

The reaction to histamin of excised arterial rings from twenty-seven steers was found without exception to be contraction. The threshold dose was from 1 part in $2\frac{1}{2}$ millions to 1 part in 500,000. He demonstrates a "cumulative" action of the drug in that repetition of a dose which failed to give rise to contraction succeeds in doing so after an interval of thirty minutes. Acetylcholin is effective in contracting the coronary arteries in approximately $\frac{1}{40}$ the dose of histamin, but no "potentiation" of the one drug by the other was demonstrable.

STEELE.

McGuire, Johnson, Hauenstein, Virgil, and Shore, Rose: Cardiac Output in Heart Disease Determined by the Direct Fick Method, Including Comparative Determinations by the Acetylene Method. *Arch. Int. Med.* 60: 1034, 1937.

The cardiac output has been determined by the direct method of Fick and the modified acetylene method of Grollman for six patients with serious heart disease. In all the patients the cardiac output was subnormal.

The results demonstrated close qualitative comparison between the modified acetylene and the direct method, although the absolute values tended to be lower by the acetylene method.

No relationship between the severity of symptoms or the severity of failure, as judged by measurements of circulatory efficiency, and the level of cardiac output was demonstrated.

AUTHOR.

Van Liere, Edward J., and Sleeth, Clark K.: Immediate Effect of Tincture of Digitalis on Emptying Time of Human Stomach. *Arch. Int. Med.* 61: 83, 1938.

It was found that 5 c.c. of tincture of digitalis when mixed with a standard test meal (consisting principally of 15 gm. of farina) decreased the normal emptying time of the stomach on an average of 18.5 per cent in seven healthy young men. The results all lay in the same direction, and there were no exceptions. In no case was the decrease in the emptying time less than 12.9 per cent, and the greatest decrease noted was 24.6 per cent.

The conclusions which may be drawn from the work reported here are as follows: Tincture of digitalis administered in doses of 5 c.c. is capable of decreasing the emptying time of the stomach of the average person about 18 per cent, as based on experiments performed on seven subjects. It may thus be given immediately before or directly after a meal without any deleterious effect on gastric motility. Experimental evidence is offered which throws light on the causation of the diarrhea which often accompanies the administration of digitalis. Finally, since digitalis is often given in conditions associated with anoxemia, which has been shown to inhibit gastric motility, the fact that it is capable of decreasing the emptying time of the stomach is of practical importance.

AUTHOR.

Hubensack, E.: The Alteration of the Electrocardiogram in the Course of Diphtheria. *Ztschr. f. Kreislaufforsch.* 29: 434, 1937.

A study based on 620 proved cases was made. Not all electrocardiographic abnormalities in diphtheria are associated with clinical manifestations of heart damage. When the electrocardiogram is abnormal, tachycardia is usually present and persists as long as the electrocardiogram remains abnormal. Conduction disturbances of any variety can occur. The mortality is high in those cases with total heart block and slow ventricular rate. Patients with other types of electrocardiographic abnormalities tend to recover. There is need of long-continued follow-up studies to determine whether in recovered patients any residue of heart damage remains.

KATZ.

Wollheim, E.: A New Depressor Substance Elaborated by the Body and Its Meaning for Essential Hypertension. *Acta med. Scandinav.* 91: 1, 1937.

The present report describes studies conducted upon the thermostable vaso-depressor obtained from normal urine, since the time it was first described by Wollheim and K. Lange in 1932. Urines from 225 normal and 102 hypertensive individuals have now been studied, each on at least five or ten separate occasions. Tests for depressor effect were carried out on rabbits.

The substance was found to be present in normal human urine, except rarely in an occasional sample, and in the urine of horses. It is absent from the urine of individuals suffering from essential hypertension or present only in small amounts in less than 8 per cent. In acute and chronic nephritis the material is present in the usual amounts, and the urine of pregnant women is rich in it. A substance quite similar in chemical and pharmacologic properties can be obtained also from the posterior lobe of the pituitary gland.

This thermostable substance, labelled by the author "depressan," can be distinguished from all of the previously described depressor substances found in the urine by its behavior on boiling with acid and alkali, by its peculiarities toward the usual dissolving and precipitating agents, by use of dialysis and electrodialysis. One liter of urine yields from 0.2 to 0.5 gm. of dry substance.

The physiologic activity of the substance either from the pituitary gland or from the urine depends upon dilatation of the peripheral vessels of from 20 to 50 per cent as measured by rate of perfusion of the rabbit's ear. The author states that the widening of the vessels is independent of the nerve supply. Reaction of heart, respiration, or intestinal muscle was not observed.

The duration of the depressant action is relatively long, depending, as does the extent of fall in blood pressure, upon the dose. In atropinized rabbits 1 mg. intravenously was followed by a fall of 20 mm. Hg for five to ten minutes and 40 mg. by a fall of 50-70 mm. Hg for one to two hours. The duration of its action is another point in differentiation from other substances.

The intramuscular injection of the substance into 18 patients with hypertension resulted in a fall of blood pressure in 14, beginning six to twelve hours after injection and lasting for from one to three days. The systolic pressure fell 30-50 mm. Hg, the diastolic about 20. The dose used was 1 c.c. (if the solution was made up according to that used for tests in rabbits, the amount of dry substance should have been roughly 100 mg.). Four patients failed to respond. Two of these were instances of severe nephrosclerosis. There is no mention of having administered the substance to normal individuals. The author believes that essential hypertension is called into being through a lack of "depressan."

STEELE.

Schellong, F., Heller, S., and Schwingel, E.: The Vector Diagram—A New Method of Studying the Heart. I. *Ztschr. f. Kreislaufforsch.* 29: 497, 1937.

The authors describe a method utilizing two cathode ray tubes connected to three leads, in such a way that one cathode ray tube depicts, as a standing wave on the fluorescent screen, the spatial distribution of the vector of the electrical axis on the frontal plane and the other the vector of the electrical axis in the sagittal plane of the body. These are called the vector diagrams of the heart. These permit one to reconstruct the spacial distribution of the changes in the electrical axis of the heart during a heart cycle, either in two or three dimensions. Since it records something different from the electrocardiogram, the vector diagram will not displace but will supplement the electrocardiogram and will be found, so the authors believe, clinically useful when developed on an empirical basis. Changes in contour of the vector diagram may be found of value in differentiating various cardiac conditions.

KATZ.

Schellong, F., and Schwingel, E.: The Vector Diagram: II. Meaning of Slurring and Splintering. *Ztschr. f. Kreislaufforsch.* 29: 596, 1937.

The vector diagram recorded spatially or stereoscopically shows that some instances of slurring and notching are benign and due merely to a change in the position of the heart, while others are found to indicate disturbances in the spread of the impulse.

KATZ.

Otto, H.: Myocardial Involvement in Tonsillitis. *Ztschr. f. Kreislaufforsch.* 29: 471, 1937.

The damage to the heart in tonsillitis is sometimes demonstrable in the electrocardiogram, as a prolongation of P-R and QRS intervals, as S-T depression, as flattening or inversion of T, as a split P, as a Q_z , as low "voltage" or as more advanced A-V block. Such evidence was found in 63 per cent of 336 cases studied. Tonsillectomy tended to decrease the electrocardiographic abnormalities.

KATZ.

Misao, T., Maêda, N., Tanaka, T., Noma, K., and Itoh, S.: *The Electrocardiogram in Agonal States of Man.* *Ztschr. f. klin. Med.* 130: 332, 1936.

In the agonal state, P-R, QRST, and QRS durations increase. This occurs despite acceleration of the heart. The S-T becomes depressed, and the arrhythmias in this state are variable. Most commonly sinus standstill is found, followed by idioventricular rhythm, ventricular standstill, or ventricular fibrillation. Fibrillation may be temporary, the idioventricular rhythm being restored and standstill occurring terminally. In other cases, the sinus rhythm persists and A-V block occurs. Rarely, the normal mechanism persists until standstill. Extrasystoles and auricular extrasystoles are rare.

KATZ.

MacMahon, H. Edward: *Hypertrophy of the Heart in Infants.* *Am. J. Dis. Child.* 55: 93, 1938.

A review of the types of cardiac hypertrophy in infants clearly shows that many different factors may play important etiologic rôles. Furthermore, when considered from a structural standpoint, the histologic picture is likewise variable. One change has been almost universally emphasized, namely, an increase in the size of the individual muscle fibers, whether in true hypertrophy or in a mere pseudohypertrophy resulting from the storage of glycogen. The purpose of this brief report is to point out that in cardiac hypertrophy appearing at an early age, in addition to the increase in size of the muscle fibers, there may be a true proliferation of these elements. A corollary to this is the suggestion that since proliferation of the fibers of the cardiac muscle may occur in hypertrophies of this group, it is possible that during the same period myocardial regeneration following severe injury may likewise occur.

AUTHOR.

Gloyne, S. R., and Shiskin, Cecilia: *Mitral Stenosis and Pulmonary Tuberculosis.* *Tubercle* 18: 394, 1937.

Mitral stenosis and pulmonary tuberculosis in autopsy records of Victoria Park for the last sixteen years contain 121 cases of mitral stenosis in only one of which pulmonary tuberculosis also occurred. From this and other records quoted, the following deductions may be made:

1. Cases of mitral stenosis rarely exhibit active lesions of pulmonary tuberculosis.
2. There were no cases showing old fibrotic or healed lesions of pulmonary tuberculosis.

Three pathologic explanations of the infrequency of this combination of diseases may be suggested:

1. That there is a true cellular and humoral immunity against tuberculosis, due to an excess of blood in the pulmonary circulation which may increase phagocytosis and even neutralize the products of bacterial metabolism. A similar hypothesis has been made to explain the beneficent effect of artificial pneumothorax. Tilsen also suggested that there was a "rheumatic diathesis" in mitral stenosis which was inimical to tuberculosis.

2. That pulmonary congestion results in pulmonary fibrosis which protects against tuberculosis.

3. That there is an alteration in the hemorespiratory exchange. Of these numerous changes, oxygen desaturation, increased carbon dioxide arterial tension, and deviations in pH value of the blood have all been cited. One of the authors

(C. S.) recently investigated this point in connection with a research on the pH values of venous blood in cardiovascular and respiratory disease. The results obtained in mitral stenosis are given.

MONTGOMERY.

Howard, John Eager, and Barker, W. Halsey: Paroxysmal Hypertension and Other Clinical Manifestations Associated With Benign Chromaffin Cell Tumors (Pheochromocytomata). Bull. Johns Hopkins Hosp. 61: 371, 1937.

From this study of proved cases, we feel that a fairly definite clinical picture emerges by which may be evaluated the possibility or probability of the presence of a pheochromocytoma in a suspected patient. The individual most likely to have a pheochromocytoma will be one who is youthful or in early middle age, of either sex, and in good health. The attacks of hypertension may vary widely in duration from a few minutes to many hours. There will generally be no known predisposing cause initiating the attacks, although the assumption of certain positions sometimes has been observed to induce attacks, and exertion and emotional stress have been felt by some patients to be precipitating factors. The attacks are more likely to come after retiring at night, and especially in the early morning hours. The patient will probably look and feel perfectly well when not actually having an episode of hypertension, although persistent hypertension is too common in this group to be totally ignored as part of the syndrome. Should persistent hypertension exist, the same manifestations will be found in the retinal arteries, heart examination, and urinalysis as are commonly seen in patients suffering with so-called essential hypertension. Electrocardiographic findings will be of no help in the differential diagnosis, even during a hypertensive attack. A mass in the abdomen, on the side of the tumor, may or may not be palpable on physical examination; there is greater possibility of its being found either by flat x-ray plates of the abdomen or by pyelographic studies, but the correctness of the diagnosis should not be seriously questioned if no mass is detected by any of these means. After paroxysms of hypertension, albumin or sugar, or both, may possibly appear in the urine. Nothing in the way of medication has been found to influence materially the frequency, duration, or severity of the attacks. If tests are made with epinephrine or pituitrin, there will probably be found no hypersensitivity nor hyposensitivity. During the early part of an attack (associated with the rise in blood pressure) the patient will almost certainly become cold, pale, or mottled, and complain of palpitation. Quite pronounced nausea and probably vomiting are almost certain to be present and, if of long duration, especially if accompanied by hyperventilation, may lead to tetany. Very severe headache is more likely than not to be complained of. If the attack is severe or prolonged, signs of cardiac incompetence are to be looked for, such as pulmonary edema, sudden hepatic enlargement, or distended neck veins. Precordial pain with radiation to the neck, down the arms, or other areas characteristic of stenocardiac attacks is quite likely to be present. Very pronounced sweating is likely to occur either during or just after the severe episode has passed. Even without any of the symptoms listed above, the patient whose usual resting blood pressure is normal may at any time be found to have quite marked temporary hypertension. In other words, milder paroxysms of hypertension may occur without the patient's being aware of them at all, just as is observed so frequently in the early stages of so-called essential hypertension. It is perhaps worthy of emphasis, however, that in patients suffering from essential hypertension the course may be totally asymptomatic for a long period of time, whereas in this group of patients the symptoms are of sufficient severity early in the course of the disease to bring the patient to the doctor.

AUTHOR.

Longcope, Warfield T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension. *Ann. of Int. Med.* 11: 149, 1937.

A study of twenty-two cases of chronic bilateral pyelonephritis indicates that a number of complications and accessory facts may modify the usual course of this disease. As the disease advances, it is usual to find that the blood pressure rises. In ten of the fifteen patients observed during the terminal or advanced stages of the disease, the blood pressure was above 160 mm. systolic and 105 mm. diastolic. In seven cases, observed during the early stages of the disease, only one had a systolic blood pressure of over 140 mm., or diastolic pressure of over 85 mm. The hypertension was not associated with pronounced or excessive arteriolosclerosis in nine fatal cases. In three of the fatal cases, the pyelonephritis was associated with a chronic diffuse glomerulonephritis. The development of the ophthalmologic picture of retinal arteriolosclerosis and retinitis is more related to the development of the hypertension than to the presence or degree of renal insufficiency. When chronic renal insufficiency does occur, it is often associated with intermittent or persistent hypertension. The explanation for the hypertension which occurs during the later stages of pyelonephritis is not clear. The bacterium which is usually responsible for the infection in the *Bacillus coli*.

HINES.

Clerc, A., and Sterne, J.: A Case of Repeated Anginal Crises With Paroxysmal Hypertension and Vasomotor Disturbances: A Record of Medical Treatment, Two Surgical Interventions, and of the Efficiency of a Synthetic Sympathicolytic Drug. *Bull. et mém. Soc. méd. d. hôp. d. Paris* 53: 562, 1937.

A woman, 60 years old, essentially normal as to physical and laboratory examination except for arterial blood pressure of 160 to 180 mm. Hg systolic, complained of attacks of severe pain in the heart of fifteen months' duration. The attacks of "anginal crises" were observed (she was hospitalized on Oct. 3, 1934) to occur in the following manner: First, an abrupt rise in the systolic level of pressure to 220 to 240, once to 300; immediately thereafter an intense scarlet blush over face, chest, and arms, leaving the rest of the body pale; then constriction of the chest, severe precordial pain radiating to the shoulders, left arm and hand, occasionally to the right. The patient cried out with pain and pressed both hands to her chest. The attacks passed off in twenty minutes or so, recurred usually about three times in twenty-four hours, and were unaccompanied by change in heart rate or electrocardiographic disturbance. After failure of every conceivable drug—a list being given—to relieve the attacks, left stellate ganglionectomy was performed on Dec. 5, 1935, without relief for more than a few hours in spite of development of Horner's syndrome, and on March 21, 1936, the right ganglion was removed with relief for about ten days. Innumerable drugs were again tried including one preparation of Fourné and Beret, piperidino-methyl-benzo-dioxan, without relief. A second synthetic benzo-dioxan (diethyl-aminomethyl-benzo-dioxan) afforded immediate relief and after a short while almost complete disappearance of the attacks. The dose was 0.20 gm. a day in four doses, by mouth. Omission of the drug for about three days on two occasions was followed by return of the attacks. The remarkable point is that all three symptoms, pain, blushing, and paroxysmal hypertension, disappeared.

STEELE.

Clark, Eugene, and Kaplan, Bernard I.: Endocardial, Arterial, and Other Mesenchymal Alterations Associated With Serum Disease in Man. *Arch. Path.* 24: 458, 1937.

Two patients who had received large doses of antipneumococcus serum died after having typical symptoms of serum sickness, one of heart failure, the other of exten-

sion to another lobe and of hemorrhage. In both cases at autopsy inflammatory arterial and periarterial lesions were found. The structural alterations in these cases consisted of proliferation of histiocytes in the neural and valvular endocardium and in the intima of the aorta and the pulmonary interstitial mesenchymal tissue of the myocardium and other viscera. Necrotizing arteritis and periarteritis of the smaller coronary arteries formed a prominent finding in one case. It is felt that the composite picture presented by these two cases is incompatible with any disease hitherto described and that they are related to the administration of foreign serum.

MONTGOMERY.

Karsner, Howard T.: Primary Inflammation of Arteries. *Ann. Int. Med.* 11: 164, 1937.

In addition to secondary inflammation of arteries due to extension of local inflammation or direct invasion, there is an inflammation which can be appropriately described as a primary arteritis. The causes of this form of arteritis are unknown or are ill-defined. The lesions found in primary arteritis have been classified and consist both of acute and chronic varieties. The chronic form is characterized by distribution of fibrosis in the three coats of the arteries and by delayed or absent secondary changes in the fibrous tissue. An improved nomenclature for the various types of arteritis would aid in correlating descriptive morphologic and clinical data so that the disease may be better understood.

HIXES.

Bordley, James, III, Grow, Max H., and Sherman, William B.: Intermittent Blood Flow in the Capillaries of Human Skin. *Bull. Johns Hopkins Hosp.* 62: 1, 1935.

The flow of blood in the minute vessels of the skin of the human leg may be clearly seen under natural resting conditions.

The circulation in individual capillaries of this area is frequently intermittent.

Intermissions in flow may occur alternately in two capillaries arising from the same arteriole.

When the flow ceases in a capillary, even during venous congestion, the vessel may become almost completely empty of corpuscles.

These observations indicate that individual capillaries are endowed with an occlusive mechanism which they may exert to prevent the passage of blood through their lumina.

Similar capillary behavior has also been observed in other skin areas.

AUTHOR.

Burwell, C. Sidney: The Placenta as a Modified Arteriovenous Fistula, Considered in Relation to the Circulatory Adjustments to Pregnancy. *Am. J. M. Sc.* 195: 1, 1938.

The demonstrated phenomena of the circulation in pregnant women plus the evidence offered by the structure of the placenta lead to the following conclusions:

The changes in the circulation during pregnancy are in the main to be ascribed to two mechanisms: (1) obstruction to venous return by the enlarged uterus, and (2) an arteriovenous leak through the placenta.

AUTHOR.

Snellen, H. A., and Nauta, J. H.: Roentgen Diagnosis of Coronary Calcification. *Fortschr. a. d. Geb. d. Röntgenstrahlen*. 56: 277, 1937.

The authors point out the ease of diagnosing calcification of the coronary arteries by x-ray. This diagnosis was reported forty times in a year with calcification of the aorta or mitral rings showing simultaneously in six cases. In five instances there was necropsy confirmation of the roentgen-ray diagnosis. The diagnosis is made by dancing shadows in the location where arteries run, the patient holding his breath in deep inspiration. Kymography was found to be of great assistance.

KATZ.

DeTakata, Géza: Sympathectomy for Peripheral Vascular Disease. *Arch. Int. Med.* 60: 990, 1937.

One hundred and twenty-six sympathectomies were performed on fifty patients. Twenty-four of these patients, with forty-six sympathectomies, have been followed for one to seven years. There were 16 operations in Raynaud's disease, 22 in Buerger's disease, 3 in poliomyelitis, and 5 in reflex dystrophy. Thirty were considered successful, 9 as improved, 6 as failures, and 1 patient died of coronary occlusion. Recently preganglionic section, as advocated by Smithwick, Freeman, and White and Telford, was used in operations for the upper extremities. Those patients who were found to have vessel spasm, as shown by heat tests or by vasodilator drugs, responded in most instances in a satisfactory way. Mistaken diagnosis, mistaken indications, improper stages of vascular disease, faulty technique, improper after-treatment, and poor follow-up are important factors in obtaining poor results. The surgeon who performs sympathectomies must be thoroughly familiar with peripheral vascular disease and its remissions and exacerbations and should use, either alone or in collaboration with physicians well versed in peripheral vascular disease, all the medicinal aids and physical therapy available at present.

MONTGOMERY.

Armstrong, Harry G.: The Blood Pressure and Pulse Rate as an Index of Emotional Stability. *Am. J. M. Sc.* 195: 211, 1938.

A review of 700 examinations of candidates for flying training for the United States Army Air Corps shows that there are correlations of 0.98 for the stable group and 0.88 for the unstable group and a general correlation of 0.92 between the relative emotional stability of the individuals and their cardiovascular findings.

This correlation was obtained by adopting an arbitrary blood pressure level of 134/90 (+ or -3) and a pulse rate of 90 (+ or -3) and assuming that any reading above that level demonstrated a relative emotional instability.

The failures of previous workers to demonstrate a high degree of correlation between emotional stimuli and cardiovascular reactions and certain other inconclusive evidence and disagreements in the literature are explained by an analysis of the reaction patterns of the author's cases into five distinct groups, wherein it was shown that among the unstable candidates 21 per cent showed no abnormal blood pressure pattern and 66 per cent showed no abnormal pulse pattern. These dissimilar reaction patterns show the fallacy of mass statistics in such studies and demonstrate the necessity of studying the cardiovascular system as a whole in each individual in psychosomatic investigations.

The limitations and shortcomings of the described test for emotional stability are pointed out, as well as a suggestion for further studies which are necessary before the test is applicable to any situation other than the one from which the test was derived.

AUTHOR.

O'Neil, E. Everett: Suction-Pressure Therapy in Peripheral Vascular Disease. New England J. Med. 217: 828, 1937.

Eighty cases of occlusion of the peripheral arteries treated by alternating suction and pressure have been reviewed. The best results were obtained in acute occlusion, when treatment was instituted before tissue changes had progressed too far. The poorest results were observed in arteriosclerosis of the extremities where diabetes was a complicating factor, and particularly where calcification of the arteries was shown by x-ray, denoting a low collateral potential. Negative-positive pressure treatment is of definite value in the early and moderately advanced cases of peripheral arteriosclerosis and thromboangiitis obliterans, exerting a marked beneficial influence on intermittent claudication and ischemic pain in these cases. Its value in the later stages is doubtful. In all types of chronic peripheral obliterative diseases to which suction-pressure therapy may be applied, it must be stressed that long periods of treatment are necessary for success. Since the tendency of any occlusive disease is to progress, it is important to keep ahead of it by frequent and continued applications of treatment.

MONTGOMERY.

Collens, W. S., and Wilensky, M. D.: Intermittent Venous Occlusion in Treatment of Peripheral Vascular Disease: An Experience With 124 Cases. J. A. M. A. 109: 2125, 1937.

Compression of the proximal portion of the extremity up to 80 mm. of mercury for alternating periods of two minutes with two minutes of release applied continuously for as much as twelve hours a day had a decided therapeutic effect in the treatment of diseases associated with pathologic arterial changes. Early reports of this method have already appeared. The authors feel that the method is capable of increasing vascular capacity, as is evidenced by the following phenomena: relief of rest pain, increased walking capacity, regeneration of tissues, improvement in the nutrition of nails, and the growth of hair over areas which had become denuded as the result of obliterative arterial disease. They were able to note in one case the development of granulation tissue to such a degree of exuberance that it necessitated the use of silver nitrate on three different occasions in order to prevent the development of keloid.

MONTGOMERY.

Erratum

In the article, "Electrocardiographic Changes Occurring With Alterations of Posture From Recumbent to Standing Positions," by Louis H. Sigler, M.D., which appeared in the February issue of the JOURNAL, in Table I, on page 150, the last figure in the last column should be 4.0 (%) instead of 0.4 (%), as it now stands.

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Original Communications

A COMPARISON OF PERCUSSION AND RADIOGRAPHY IN LOCATING THE HEART AND SUPERIOR MEDIASTINAL VESSELS*

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STATEMENTS in anatomical and clinical textbooks regarding the position of the cardiac borders commonly have several defects: failure to distinguish between the living subject and the cadaver, failure to make allowance for normal variation, and failure to indicate what or how many subjects provided the average figures that are quoted. Certain cardiologic data fulfill these requirements, but cannot be used as standards in percussion unless the discrepancy between percussion and radiologic observations is well known. In our department percussion is used as a method of "dissecting" the living body, and the question of its error has naturally arisen. Although many informal investigations on this must have been carried out, there do not appear to be many published reports. Examples are those of the following authors:

Bisbini,¹ after comparing orthodiagraphy and five percussion methods on eleven persons, concluded that percussion figures were often a little smaller than those obtained by orthodiagraphy. The data show that greater allowance for variation ought to be made than the author apparently realized.

Kurtz and White² compared telcoradiography and percussion on one hundred patients (adults and children, males and females). Their data suggest that the low average percussion error and insufficient analysis of variation led to the conclusion that percussion was "reasonably accurate."

Wilson³ made a general statement of Gordon's special study, and his conclusion was that the percussed outline agreed with the roentgenogram if the patient was standing, but was quite unreliable in recumbency.

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Further investigation is justified by the not uncommon distrust of percussion piquantly expressed by Wilson,⁸ and by the fact that, percussion being an art, detailed studies by many observers are necessary for a verdict on its general reliability.

OBJECTS OF THIS INVESTIGATION

"Percussion error" is used here in its clinical sense, as meaning the difference between percussion results and those of teleoradiography, the latter method being accepted as the standard, more reliable than percussion, but not necessarily perfect. Our objects were (1) to find the discrepancies between teleoradiography and one common percussion method used by an experienced physician (not a cardiologist) under favorable conditions, that is, avoiding females because of the mammary gland, diseased subjects, and stout middle-aged or old men; (2) to search for factors such as chest shape that might enable one to estimate the percussion error in an individual patient; (3) to show what a practitioner could learn of his own percussion error from a small inexpensive series of films.

SUBJECTS AND METHODS

One hundred ten Dalhousie University male students were used; their ages ranged from 19 to 25 years, except for three between 25 and 32 years. Some were Anglo-Saxons, others American Hebrews of varied European ancestry. In all students the same physician found the deep dullness of:

(a) the superior mediastinal vessels and heart in the first five intercostal spaces on the left;

(b) the heart in the fourth right intercostal space;

(c) the liver, approached from above, in the right midclavicular line. The physician placed his left middle finger flat on the chest parallel to the border of the organ that he was approaching, and struck the terminal phalanx of this finger by the tip of the right middle finger. He marked by skin pencil the dullness at each of the points mentioned above and fastened by adhesive tape along the pencil mark a brass wire $\frac{1}{2}$ to $\frac{3}{4}$ inch long and $\frac{1}{32}$ inch in diameter.

During percussion and filming, the students were always in the mid-phase of respiration with their arms loosely at the sides of their bodies. Each student was first percussed erect, and then a heart radiograph was taken with the student's anterior thoracic wall against the film holder, the x-ray tube (G.E.C. line-focus, mechanically rectified, 100 Ma., 100 kv.) being 6 feet from the film and centered about the fifth and sixth thoracic vertebrae. The wire markers were then removed from the chest wall, the student lay down, percussion was repeated, new wires were attached, and a radiograph was taken with the film beneath the student and the x-ray tube 6 feet above the film.

On all the films one observer (C. B. S.) measured with calipers, to the nearest millimeter, the perpendicular distance from the center of the shadow of each wire to the adjacent border of the heart, vessel, or liver. If the wire representing deep dullness lay within the shadow of the organ, the measurement was marked +, if outside the shadow, -.

Biometrical analysis of such data is necessary, and the frequency distribution of the errors, as in Fig. 1, was of the "cocked hat" type, sufficiently like a statistically normal curve to justify testing the results by normal curve methods. We adopt the usual convention regarding the significance of differences previously discussed in another connection (Mainland⁵) and more fully treated elsewhere (Mainland⁷),

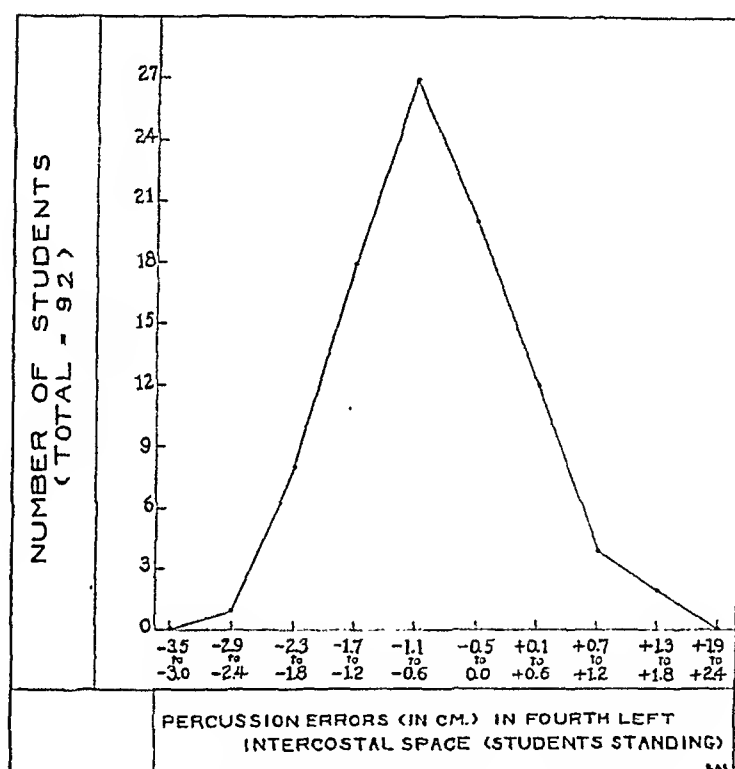


Fig. 1.—Frequency distribution of percussion errors.

along with the other statistical methods mentioned below. (It should be specially remembered that "significant" does not imply "important.")

MEAN PERCUSSION ERROR

Erect Position.—The mean percussion errors in intercostal spaces L 1 and L 2 (Table I) are less than twice their standard errors and therefore not significantly different from zero. In the other spaces the means are all much more than three times their standard errors, and this is very strong proof that under the given conditions the shadow of the percussion marker tends on the average to be lateral to the radiographic border in spaces L 3, L 4 and L 5 by over half a centimeter, and in space R 4 medial to the radiographic border by about $1\frac{1}{3}$ cm.

Recumbent Position.—Except in L 2, all the mean differences are definitely significant. In each space they are in the same direction (+ or -) as in the erect position. For each student the error was compared with the corresponding error in the erect position, and in the upper four left spaces there was no marked discrepancy between the two positions, but in L 5 and R 4 the errors were significantly greater in recumbency. The average differences are shown in Table I.*

TABLE I
PERCUSSION ERRORS IN PRINCIPAL SERIES OF STUDENTS
(The + and - Signs Are Used as Stated in the Text)

INTERCOS- TAL SPACE (RIGHT OR LEFT)	STUDENTS STANDING ERECT				STUDENTS RECUMBENT			
	NUM- BER OF STU- DENTS	MEAN ERROR (CM.)	STANDARD DEVI- ATION OF SERIES OF ERRORS (CM.)	STANDARD ERROR OF MEAN (CM.)	NUM- BER OF STU- DENTS	MEAN ERROR (CM.)	STANDARD DEVI- ATION OF SERIES OF ERRORS (CM.)	STANDARD ERROR OF MEAN (CM.)
L 1	93	+0.157	0.803	0.083	94	+0.262	0.826	0.085
L 2	93	+0.057	0.886	0.092	94	+0.157	1.036	0.107
L 3	93	-0.579	0.912	0.095	94	-0.435	1.190	0.122
L 4	92	-0.661	0.907	0.095	93	-0.711	1.074	0.111
L 5	90	-0.582	0.970	0.102	85	-1.307	1.112	0.121
R 4	93	+1.302	0.950	0.098	94	+2.110	1.031	0.106

If sign and degree of error are considered, Table I suggests a certain trend from space L 1 downwards in both erect and recumbent positions, and, in spite of irregularities, a regression test showed that this was more than is usually attributed to chance. In the upper spaces percussion (in recumbency at least) failed to detect the dullness as soon as it should, according to the radiographic shadow, and below that there was a tendency for the dullness to be detected farther and farther away from the radiographic margin. The results of Kurtz and White⁴ suggest a similar tendency.

VARIATION IN PERCUSSION ERROR

A low or negligible mean error does not indicate that a method is reliable. The important question is: By how much does the error vary (a) from subject to subject and (b) in repeated examination of the same subject? The variation between students is expressed by the standard deviations in Table I—between 0.80 and 1 cm. in the erect position and rather over 1 cm. for most spaces in recumbency. In such applied biologic work as this, it is customary to use as a measure of uncertainty twice the standard deviation on each side of the mean. If

*Kurtz and White⁴ decided that there was no great difference between the error in the erect and recumbent positions. It is not clear whether their averages were formed by summing without regard to + and - signs, but the general average of their hundred subjects may be quoted here for comparison: Space L 4, 5, or 6: 0.6 cm.; L 3: 1.2 cm.; L 2: 1.3 cm.; R 4: 0.8 cm.

Our general conclusions regarding the absence of great discrepancy between erect and recumbent errors agree with those of Kurtz and White⁴ rather than with those of Gordon as reported by Wilson.⁵

a physician whose percussion has the variability represented in Table I finds in an erect patient the deep cardiac dullness in space L 4, he has obviously no right to the confidence that the low mean error suggests. For all he can tell, a film taken under the conditions of our investigation may show the radiographic border anywhere from about 2.5 cm. medial to his percussion marking up to 1 cm. lateral to his marking, and in about 5 per cent of patients the difference will be outside even these limits. The actual data used in Fig. 1 confirmed these estimates, and estimates for the other spaces can be made in the same way.*

FALLACIES AND POSSIBLE CAUSAL FACTORS

1. *Dispersion of X-Rays.*—Although radiologic results were adopted as our standard because they are known to be more accurate than percussion, x-rays, even with the tube 6 feet from the film, are not parallel,

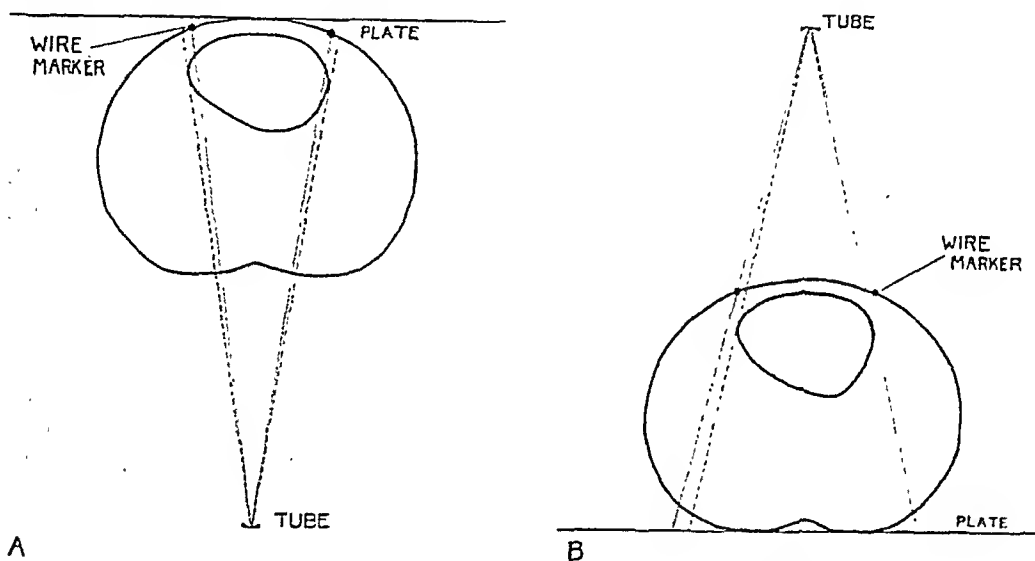


Fig. 2.—Outlines of thorax and heart to show effect of dispersion of x-rays.

A, Students erect; B, students recumbent. Plate = film holder.

(The distances between tube and thorax are diminished out of proportion to the thorax size, to fit into the diagram.)

and the question arose: Could the dispersion of the rays account for the mean percussion errors, or for the differences between the mean errors in the two positions of the body?

Fig. 2 shows that, if percussion identified exactly the borders of the heart or vessels, their shadows would overlap the shadows of the wires in the erect position (A), but in recumbency (B) the reverse would be true. In both positions, however, the direction (+ or -) of the corresponding errors was the same (Table I). Therefore the dispersion of the rays could not account for the errors, although it would necessarily affect their numerical values.

*It is unfortunate that the variations in the series of Kurtz and White⁴ are expressed only as maximum values outside and inside the heart shadow. In 42 adults their maxima were: Space L 5, 2.1 cm. outside and 1.7 cm. inside; space L 3, 1.1 cm. outside and 3.4 cm. inside; space R 4, 1.1 cm. outside and 4.4 cm. inside. These figures suggest that more detailed data or a more adequate expression of the variation might reveal variation similar to that of our series.

Thirty wires, $\frac{1}{64}$ inch in diameter, were mounted at 1 cm. intervals on plywood, and a radiograph of this with the tube 6 feet from the film showed that the following allowance should be made for magnification: For an object (cardiac border or wire) at 5 cm. from the film, 3 per cent; at 14 cm., 8.5 per cent; at 19 cm., 11.5 per cent. It was sufficient for our purpose to apply these figures to the mean antero-posterior thoracic diameter of the students (19 cm. at the fourth costal cartilage) and to use the relative positions of the heart and chest wall given by dissecting room material and anatomical pictures. The results showed that, if there were no dispersion of rays, the percussion error in space L 5 (erect) would be of the order of -0.8 cm. instead of -0.582 cm. (Table I) and -1 cm. instead of -1.307 cm. in the same space in recumbency.

These calculations, although rather rough, showed that the discrepancy in space L 5 between the mean errors in erect and recumbent positions could be accounted for largely, or perhaps wholly, by dispersion of rays. It was doubtful whether the discrepancy in space R 4 could be entirely so explained. Differences in the distance between the heart borders and chest walls in different students might account for some of the variation in error and for some of the difference in variation between the erect and recumbent positions, but we had not sufficient profile radiographs to show this. It was beyond our purpose to pursue this question farther, and the corrections just mentioned need not be considered in the subsequent analysis of the errors.

2. Change of Position of Wires Between Percussion and Filming.—For various reasons, chiefly the physician's and radiologist's lack of spare time, it was practically impossible, except on a few students, to measure the position of the percussion markers on the students' chests before filming. Moreover, to secure quietness, percussion was done in a small room several yards from the x-ray room, and the students had to walk into the latter and take up the proper position again for filming. It was therefore necessary to ask: How far did the change in position of the wires due to respiration or skin movement introduce an apparent percussion error?

The midphase of respiration does not secure exactly the same degree of chest expansion on any two occasions, but we should expect that the difference would be as likely to decrease as to increase the percussion error and therefore would make little difference in the mean error. The respiratory movement of the wires might, however, increase the variation in errors, and this possibility was specially examined. On the chests of ten students (Special Series I), percussed erect, measurements to the nearest millimeter were made from the median plane to the percussion wires. On the films, taken after the students had moved about and breathed, the measurements were repeated in each of the six spaces as in Table I, the median plane being determined by the shadows of

wires that had been placed vertically at the center of the upper border of the manubrium sterni and at the center of the xiphisternal joint. All the films showed two or more intercostal spaces in which the thoracic and film measurements differed by no more than 1 mm. In spaces L 1 and L 4 the percussion error was estimated (a) from the thoracic measurements and (b) from the film measurements. The two estimates showed no significant differences either in mean errors (tested by the *t* formula) or in standard deviations (tested by the *z* formula). (For the technique of these tests see Fisher,² and for a more elementary exposition see Mainland.⁷)

In another ten students (Special Series II) percussion was done at the x-ray equipment, and the first film was taken with a minimum amount of movement after percussion. A second film, with the same wires in place, was taken after the student had moved about and had breathed several times. Special attention was paid to the distances between the wire shadows in space L 4 and the median plane, and the change in these from the first film to the second was found to be similar to the differences in Special Series I. More convincing still was the lack of a significant correlation between the change in the percussion error and the movement of the wires. There is therefore no apparent reason to reject the results of Table I because of movement of wires between percussion and filming.

3. *Change in Size of Heart Shadow.*—In Special Series II the differences between the percussion errors in space L 4 (erect) on the first and second films were compared with the change in transverse diameter of the cardiac shadow. The coefficient of correlation (0.725) was significant (Fisher²) and showed that the narrower the heart became, the more its left border tended to depart medially from the percussion marker. The importance of this hardly surprising fact was indicated by further investigation. The change in heart shadow might be attributed to the following factors:

A. The phase of cardiac contraction, which is said to alter the size of shadow by 2 to 7 mm. (Köhler³). As we had no means of investigating this we turned to other factors.

B. Rotation of the thorax. On the main series (films of ninety students) an indication of chest rotation was obtained by measuring the distance between the sternal midline, shown by shadows of wires placed there before filming, and the vertebral midline, seen on the films. There was no significant correlation between the percussion error (in space L 4, erect) and this measurement of rotation.

C. Change in position of diaphragm. In Special Series II of duplicate films the change in height of the left dome of the diaphragm between the first and second films was found by reference to intervertebral spaces. In intercostal space L 4 the coefficient of correlation between the change in percussion error and the change in diaphragm height

was 0.891—a highly significant value. When the marker in the first film was to the left of the heart shadow (a negative error according to the convention used in Table I), this error was increased in the second film in proportion to the descent of the diaphragm; and when the marker in the first film was to the right of the heart border (a positive error), descent of the diaphragm was associated with a corresponding decrease of the error. This correlation could not be attributed to movement of the wires laterally during inspiration because the coefficient of correlation between the diaphragm movement and the change in position of the wire shadows, measured from the midsternal line, was nonsignificant (0.586), as was also the coefficient of correlation between the wire movement and the change in percussion error (0.599).

Therefore the correlation between diaphragm movement and change in percussion error can be reasonably interpreted as a causal relationship. The descent of the diaphragm caused a medial movement of the left border of the heart, and an ascent of the diaphragm, the reverse, with corresponding changes in the percussion error. The effect of movement of the diaphragm on the position of the cardiac borders is well known, but this analysis has shown its importance even when the subject is in the midphase of respiration on each occasion, and the numerical relationship enables us to interpret and analyze the high variations (standard deviations) in Table I.

In Special Series II (erect) the coefficients of correlation between diaphragm movement and change in percussion error were estimated for other intercostal spaces in the same way as for space L 4. The coefficients were:

L 1: 0.283	L 4: 0.891
L 2: 0.233	L 5: 0.707
L 3: 0.742	R 4: 0.880

The first two are not significant, that is, there is no evidence that diaphragm movement has any effect on the variation in percussion error in the upper two spaces. The other coefficients are all significant. This Special Series II was equivalent to a random sample of the students of Table I, and by a well-known technique (see, for example, Mainland⁷) the coefficients can be applied to Table I to estimate what would have been the standard deviations (in centimeters) if no diaphragm movement had occurred between percussion and filming:

L 3: ± 0.61	L 5: ± 0.69
L 4: ± 0.41	R 4: ± 0.45

In spaces L 4 and R 4 the variation has been reduced by more than half, in the other two spaces by about one-third.

Two points should be noted regarding these modified figures:

a. The standard deviations in Table I, compared with these reduced values, indicate how percussion increases the variation which is found in x-ray technique itself; this variation arises because diaphragm movement introduces discrepancies between different radiographs taken from the same person, owing to the difficulty of securing the same mid-phase of respiration on successive occasions—a difficulty that is well recognized by radiologists.

b. Improvement of percussion technique cannot eliminate the variation due to diaphragm movement, but repetition of observations can reduce it. If the variation between percussion errors in a certain intercostal space in the same patient (see below) is represented by a standard deviation of 0.8 cm. and if a physician desires greater precision, he can obtain it by percussing the cardiac border several times at intervals of a minute or two, without allowing the different results to influence each other. During the intervals the patient will breathe and set himself afresh at the midphase of respiration. The mean of four such readings would have a standard error of 0.4 cm. (division of 0.8 by $\sqrt{4}$).

4. *Change in Accuracy of Physician.*—The physician did not see the films until the whole survey was completed. The percussion was done at intervals throughout four months, but no tendency towards a change in accuracy was found. Usually not more than four students were percussed on any one occasion. On three occasions when five or six were percussed, the errors were tested for fatigue effects, but none was found.

RELATIONSHIP OF PERCUSSION ERROR AND BODY MEASUREMENTS

The statures and weights were obtained from the students' health service records. The chest measurements were made, not with anthropometrical accuracy, but by a pelvimeter, so that, if they proved of value, a clinician might easily make them when percussing a patient. Coefficients of correlation were calculated to express the relationship between these measurements and the errors in space L 4, on about 90 students in each instance.

The numerical error, regardless of its direction (+ or -) had a low and nonsignificant correlation with stature, weight, anteroposterior diameter of thorax, transverse diameter of thorax, height of thorax, and subcostal angle (measured roughly by tracing on paper). When the direction (+ or -) as well as the numerical value of the errors was considered, there was still no significant correlation between the error and the body weight or the transverse diameter of the thorax. There was, however, a slight but definite tendency for the percussion marker to be placed more and more laterally with increasing stature (coefficient of correlation, $r = 0.26$), and with increase in the anteroposterior diameter of the thorax as measured at the fourth costal cartilage ($r = 0.24$). The stature-percussion relationship could not be accounted

for by the slight tendency for taller students to have deeper chests ($r = 0.21$). These slight relationships, whatever their interpretation, have no practical value, but are mentioned as of possible interest to other investigators.

An attempt was made to obtain by profile and oblique radiographs an indication of the thickness of the thoracic skeleton, muscle, and fat overlying the heart, but the results were not good enough to justify an attempt at correlation with percussion error.

VARIATION OF PERCUSSION ERROR IN THE SAME SUBJECT

Kurtz and White⁴ stated that thickness of chest wall, age, and sex did not seem to affect percussion error, but it appears to be well recognized that large mammary glands reduce the reliability of percussion, that is, reduce the observer's confidence that he will find the same results on repeating the percussion under the same conditions. We have not a large series of exact duplicates, and the survey did not include females, but our data indicate an answer to the question: Is the variation between repeated observations on the same person any less than the variation, for instance, in Table I, between different people; or is there any factor (apart from major factors, such as, perhaps, large mammary glands or intrathoracic adhesions) that tends to make the percussion error characteristic of the individual student or patient? Three sets of observations provide evidence regarding this:

1. For ninety-one of the students in Table I the error in recumbency was compared with the corresponding error in the erect position. The coefficients of correlation were: space L 1, -0.324 ; space L 4, -0.376 .

2. Through a misunderstanding, seventeen students stood for filming with their arms not properly at their sides. Percussion and filming were therefore repeated. The errors in space L 4 in the duplicate films gave a correlation coefficient of $+0.40$.

3. In the films of Special Series III the errors of the two physicians in space L 4 showed a correlation coefficient of -0.36 .

Both the coefficients in 1 are significant. Those in 2 and 3 taken separately are not, for the samples are small, but all four agree rather closely. They are not large enough to make any reduction of practical importance in the standard deviations of Table I. So far as could be demonstrated, the variation in error in repeated percussion of the same person was, for practical purposes, as great as in the percussion of different persons.

COMPARISON OF THE PERCUSSION OF TWO PHYSICIANS

On ten students (Special Series III) selected at random from those previously percussed (Table I) a second experienced physician percussed the heart and vessels and obtained films as before, but used a method in

which the tip of the pleximeter finger instead of its volar surface was applied to the chest, and the plessor finger struck the region of the terminal interphalangeal joint of the pleximeter finger. Table II shows that in the upper three spaces the second physician's error exceeded that of the first physician to a greater degree than should be attributed to chance. There was a pronounced tendency for the markers of the second physician to be lateral to the cardiovascular shadow in these spaces. It did not appear likely that these differences were due to the aorta, which may cause difficulty in the upper part of the cardiovascular shadow. In spaces L 4, L 5 and R 4 there was no significant mean difference between the errors of the two physicians.

TABLE II

COMPARISON OF PERCUSSION ERRORS OF TWO PHYSICIANS

(The Numerical Differences Were Found Regardless of Whether the Percussion Wires Were Medial or Lateral to the X-ray Borders)

INTERCOSTAL SPACE	MEAN OF DIFFERENCES IN ERROR IN TEN STUDENTS, I.E., ERROR OF SECOND PHYSICIAN MINUS ERROR OF FIRST PHYSICIAN			
	STUDENTS ERECT		STUDENTS RECUMBENT	
	MEAN DIFFERENCE IN ERROR (CM.)	STATISTICAL SIGNIFICANCE	MEAN DIFFERENCE IN ERROR (CM.)	STATISTICAL SIGNIFICANCE
L 1	+1.19	Highly significant	+0.98	Significant
L 2	+1.22	Highly significant	+1.04	Significant
L 3	+1.09	Highly significant	+0.69	Highly significant
L 4	-0.12	Not significant	-0.06	Not significant
L 5	0.00	Not significant	+0.01	Not significant
R 4	-0.21	Not significant	+0.21	Not significant

In spite of its greater mean errors, the second physician's percussion might still be the more reliable if its variation were less than that of the first physician. There was, however, no significant difference in the variation, as shown by the z test. It may be reasonably claimed that the two methods are equally satisfactory, provided that allowance is made for the differences if a patient percussed by the one physician is subsequently percussed by the other.

ESTIMATION OF PERCUSSION ERROR FROM SMALL SAMPLES

In allowing for percussion error, each physician should know the error of his own technique, and yet the expense involved may prevent his using many large films. Decisive results have been extracted above from small samples (Special Series I, II, and III), and similarly an observer may, for instance, compare two methods or test his increase of accuracy after practice. The necessary statistical techniques (t and z tests) have been specified above. They are often simpler than large-sample techniques, they are easy to learn, and the arithmetic for all the intercostal spaces need not occupy more than a page or two of foolscap.

Apart from such comparisons, however, the observer must ask: To what extent may my small-sample estimate of mean error and standard deviation differ from the "true" values of these quantities, that is, those approached by increasing my observations more and more? One example briefly discussed will suggest the answer to such questions.

One set of ten films taken at random from the main series in this investigation showed a mean error in space L 4 (erect) of -0.97 cm.; standard deviation, ± 1.45 cm.; standard error of mean, ± 0.46 cm. Therefore, on the usual convention regarding statistical significance, the "true" mean error may lie anywhere between $+0.07$ cm. and -2.01 cm. If the standard deviation remained as above, and the films were increased to 25, the possible discrepancy from the "true" mean error might, on the same convention, be ± 0.6 cm.; for a sample of 50 films, ± 0.4 cm.; and for a sample of 100 films, ± 0.3 cm.

The possible inaccuracy of the standard deviation in this sample is fully discussed elsewhere (Mainland⁷). Regardless of actual estimates, any standard deviation estimated from a sample of ten may be an underestimate by nearly 40 per cent of the "true" standard deviation; from a sample of 25, by 24 per cent; from a sample of 100, by about 12 per cent; and from a sample of 1,000, by 3 or 4 per cent.

With such knowledge the observer may decide that complete cardiac films, to be sufficient in number, would be too expensive, and that he should test his percussion by a fluoroscopic screen or by narrow strips of film to cover the region in which he has found the heart border by percussion.

SUMMARY

The deep dullness of heart and superior mediastinal vessels was percussed on 110 male university students (erect and recumbent) by one physician, wire markers were fastened to their chests, and teloradiographic films were taken. All results were analyzed statistically.

In these students the mean errors (difference between percussion and x-ray borders) were less than 1 cm. in most intercostal spaces; but much greater allowance for possible error had to be made in percussing any one individual—for example, a range of over 3.5 cm. in the fourth left intercostal space in erect students.

The differences in error between erect and recumbent positions could be largely attributed to dispersion of x-rays.

For practical purposes the variation between two percussions on the same student was as great as between different students because the correlation between the errors in repeated percussion of the same students, although significant, was low.

From one-third to one-half of the variation in the cardiac (but not the superior mediastinal) region was attributable to diaphragm move-

ment, owing to the impossibility of securing the same midphase of respiration on any two occasions.

The risk of wide error in any individual percussion could be greatly lessened by taking the average of several independent readings, thereby reducing the effect of diaphragm movement.

Stature, weight, and chest size or shape had no important relationship to the percussion error.

Ten students, taken at random, sufficed to show the difference in error of two experienced physicians.

Since each observer should know his own percussion error, the amount of information obtainable from a small series of films is illustrated.

We wish to acknowledge our indebtedness to the Banting Foundation of Toronto for financing this research, and to Dr. C. W. Holland, Dr. T. M. Sieniewicz, and Dr. C. M. Jones, of Dalhousie University, for the time and care spent in the percussion and radiology. A summary of part of the work was given at the Oxford meeting, July, 1937, of the Anatomical Society of Great Britain and Ireland (Mainland⁶), and has been incorporated herein with the permission of the Society.

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AN INJECTION PLUS DISSECTION STUDY OF CORONARY ARTERY OCCLUSIONS AND ANASTOMOSES*

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CAREFUL, important, and informing studies on the anatomy, distribution, and anastomoses of the coronary arteries in both normal and pathologic human hearts have been pursued for hundreds of years, ever since Lower first described such anastomoses in 1671. Nevertheless, to this day, in any series of hearts studied from the viewpoint of the correlation of the site of cardiac infarcts and of coronary occlusions, numerous instances of what are apparently inconsistent findings are encountered. It was our purpose to attempt to find an explanation for these apparent inconsistencies. Because of the high incidence of infarcts in the left ventricle, a region obviously supplied by the left coronary artery, most attention is usually given to this vessel. We also at first confined our attention to the study of the left coronary artery. A frequently described finding is marked narrowing or even complete occlusion of one or of several of the main branches of this artery with no definite infarct in the left ventricle, or, at most, some diffuse, microscopic myocardial fibrosis. When this is found, it has been assumed that a collateral circulation had nourished the myocardium ordinarily supplied by that part of the vessel distal to the occlusion. Attempts to demonstrate such collateral circulation by direct, unaided dissection are rarely successful.

Occasionally a heart is encountered in which a fresh infarct is present in the left ventricle, but in which an attempt at complete dissection of all the branches of the left coronary artery fails to reveal the vessel with the freshly deposited occluding thrombus. The most that is found is marked arteriosclerotic narrowing in one or several of these branches. Then one of two assumptions is made. Most commonly, spasm, with temporary complete occlusion of the narrowed zone, is postulated. From the structure of the narrowed arteries, this explanation is difficult for the histologist to accept. He is more often ready to admit that his dissecting scissors may have dislodged a small thrombus from a narrowed area. For this reason, when seeking areas of complete occlusion, some prefer to use multiple, closely spaced cross sections of coronary arteries for routine dissection.

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Noteworthy contributions, nevertheless, continue to be made by careful ordinary dissections. Thus, in the recent publication of Saphir, Priest, Hamburger, and Katz,¹ careful, complete dissection of the main branches of the uninjected coronary artery tree led to the significant conclusion that "wherever a myocardial infarct was encountered, at least two branches of the coronary arteries supplying the infarcted areas were involved." However, even by the most painstaking and time-consuming dissection, only the major branches of the coronary arteries can be opened and inspected. After performing such a dissection on the uninjected arteries and with our attention focused on the left coronary artery, we have never felt sure that no branches have been missed. Saphir and his associates¹ abandoned attempts to inject the vessels because of the possibility of dislodging or losing a thrombus. By carrying out the injection slowly and carefully and by keeping the injection pressure within physiologic limits (150 mm. Hg), we hoped to minimize this danger. In our preliminary experiments we injected hot agar, tinted with methylene blue. After such a procedure the agar quickly hardened, the injected vessels were distended, their intimas were tinted, and the dissection was much facilitated. Even after this preliminary injection of colored agar, however, the dissection could not be carried out to small vessels obviously injected and tinted.

In some of our earlier experiments the colored agar injected into the left coronary artery returned through the open right coronary artery, thus crudely demonstrating a connection between the two coronaries. Similar observations were made by Oberhelman and Le Count,² who injected mercury at a pressure of 150 mm. Hg. It soon became obvious that to untangle the inconsistencies encountered in connection with occlusions of the branches of the left coronary artery, it would be necessary to use a method capable of completely and simultaneously visualizing the entire coronary artery tree in a manner such that the whole course of each individual arterial branch could be studied for defects, narrowing, occlusions, or anastomoses. Karsner³ called attention to the inadequacy of the available methods for this purpose.

In modern times three types of procedures stand out as having yielded the most information in the hands of different workers. These are all modifications of methods used by numerous previous investigators. The monographs of Gross,⁴ of Spalteholz,⁵ and of Whitten⁶ give an adequate and complete review of the literature of the various methods previously used.

Gross⁴ injected the coronary arteries with a suspension of barium sulfate in warm gelatin, fixed the heart *in toto* in formalin, and took stereoscopic roentgenograms. Because of the overlapping of the vessels from the various planes of the heart, interpretation of such films is very difficult. Even the stereoscopic view of such films leaves one much in doubt about anastomotic channels. Because of its crescentic shape, this

is especially true of the vessels of the interventricular septum. On the other hand, occluded branches can be very easily overlooked. In an attempt to overcome these difficulties, Gross and Kugel⁷ have recently modified the original method by slicing the injected and fixed heart and then taking stereoscopic roentgenograms of the slices.

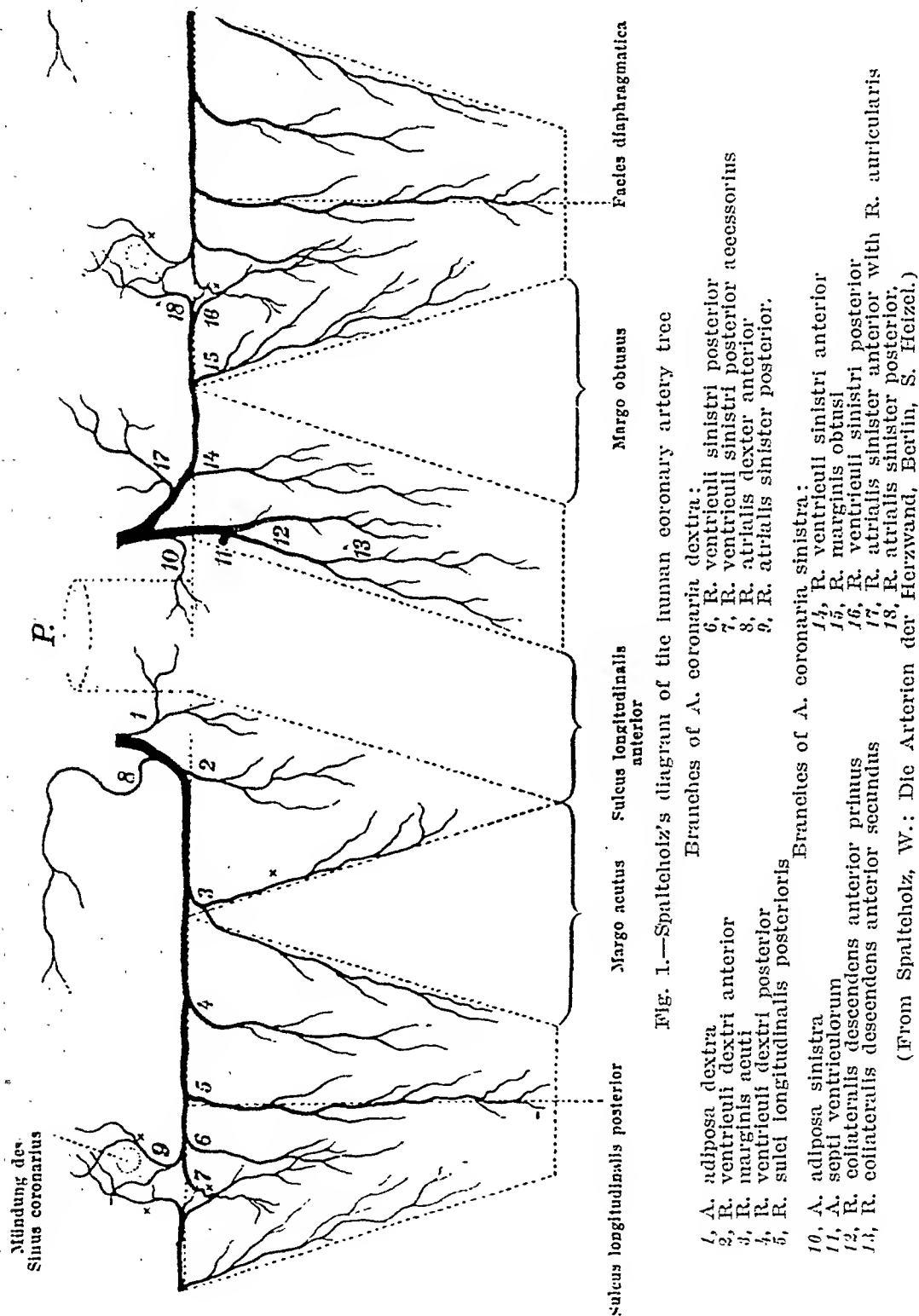
Spalteholz,⁵ after injecting the coronary arteries with gelatin in which were suspended various minerals or other opaque substances, fixed and bleached the entire heart and then cleared the specimen by a technic similar to that used for clearing small blocks of tissue for microscopic sections. The main objection to this method, as Spalteholz himself recognized, is that the clearing is often irregular and incomplete, especially in the thicker portions of the specimen. Thus one cannot be assured that in every heart he will be able to visualize in its entirety even that part of the coronary artery tree which has been injected. It is obvious that such a method is unsuitable for a complete study of the distribution of all occlusions and anastomoses in individual hearts.

Whitten,⁶ after a careful and exhaustive review of the various methods which have been used for exploring the entire vascular system of the heart, concluded that celloidin injection followed by corrosion was the most suitable. However, such a method destroys the tissue completely, and can be used only when no other studies are to be made on the heart. Most of the human hearts obtained at autopsy are too valuable to be almost completely sacrificed to one purpose. This is especially true when infarcts or other lesions are present.

The fact that one must trace a particular vessel through a maze of branches of other vessels is a disadvantage common to all these methods. This has been compared by Crainicianu⁸ to a winter scene of a street lined on either side with trees with their bare branches overlapping. Anastomoses between two trees are always apparent, although one knows it cannot be true. If this overlapping could be eliminated, the method of Gross would probably be most suitable for our purpose. Others (Crainicianu,⁸ Campbell,⁹ and Gross and Kugel⁷), recognizing the limitations of the original method, have attempted to circumvent them by dissecting out various parts of the heart, after injection and fixation, in order to obtain unobstructed roentgenologic views of selected regions for study of particular vessels. None has succeeded in displaying simultaneously all the major vessels and possible anastomotic channels without overlapping.

Spalteholz,⁵ using the data of Bianchi, devised a very useful diagram (Fig. 1) illustrating how the coronary arteries would be arranged if they could all be laid out in one plane. If, instead of making a diagram, it were actually possible to do this with each individual heart, our purpose could be accomplished. Spalteholz's diagram was made in much the same manner as a map of the earth is prepared. The conical projection method of cartography consists of the projection of a hemisphere on a hollow

cone. This cone is then cut along one of its meridians, from base to apex, and its conical surface laid out flat. Since the ventricles of the heart make a roughly conical mass and since most of the large vessels lie



close to the surface of this cone, such a procedure should be applicable to the heart. Many apparently formidable difficulties must be surmounted, however, before this simple concept can be transferred to actual practice.

In the first place, the conical mass of the ventricles is vertically transected by the interventricular septum, which lies in another conical plane. This septum carries important arterial branches whose relations to the rest of the coronary tree must be preserved. The original Spalteholz diagram and modifications of it (Saphir and his associates') make no attempt to include the vessels of the interventricular septum. This deficiency is indicated by the inclusion of a cutoff stump of a branch of the left descending coronary artery, which is labelled *A. septi ventriculorum*. This implies that the septum is entirely supplied by the left descending coronary artery, which is decidedly at variance with the observations of other investigators.

The second question was the selection of the proper meridian on which to cut the ventricular cone to give the least distortion of the picture. This incision should neither transect any large branches with their areas of occlusion nor pass through any of the common areas of possible anastomosis. Spalteholz, in his diagram, recognized this difficulty, for he duplicated a portion of the termination of both coronary arteries. Thus, he suggests cutting on a meridian corresponding to either the acute or the obtuse margin of the heart. However, the former incision would cut through the right coronary artery and the latter through the left circumflex artery. We avoided both these anatomic landmarks and cut on a meridian slightly to the right of the anterior interventricular sulcus. This is a relatively "silent area" in the heart in relation both to large vessels and anastomotic channels.

The third major difficulty is presented by the complicated pattern of valves and valve rings forming the base of the hypothetical ventricular cone (Fig. 9). Furthermore, superimposed on the base of this cone are two irregularly shaped auricles which it is also desirable to preserve. In the midst of these structures are the origins of the two coronary arteries. The position of these latter openings also influenced us in the selection of the proper meridian for our first incision. The meridian selected, when continued across the base of the cone, falls between these two openings, so that when the cone is entirely flattened out, the origins of the two coronary arteries are located at the extreme ends of the straightened out base of the cone, instead of in the middle, as in the Spalteholz diagram. It was also necessary to devise appropriate incisions to divide the auriculoventricular valves and the auricles so that these and the other important structures in the base of the heart would be left in suitable condition for the demonstration of any pathologic changes which might be present.

The success of a method involving such an unrolling of the heart with subsequent roentgenologic visualization of the previously injected arteries would depend largely upon the selection of the proper injection mass. This mass must not be intrinsically injurious to the tissues. It should be freely fluid at a temperature not injurious to the tissues. It should

have sufficient radiopaecity to allow visualization of the smallest vessels injected. It should preferably penetrate uniformly to all the smallest arterioles, but not to the capillaries. It should be of such a nature that the injection may be completed rapidly. It should be possible to harden the mass permanently and rapidly after injecting it, so that none could escape during the unrolling process. After hardening the mass, it should be flexible enough so that the heart could be unrolled without distortion. To obviate the danger of producing artifactual occlusions where none exist, it should contain no large particles. After hardening, it should be of such a consistency that it may be removed easily during the dissection of the coronary arteries. The agar solution used for our preliminary studies seemed ideally adapted to this purpose, if the proper radiopaque substance could be incorporated with it.

From the large number of radiopaque substances available, we selected a lead salt. It was to be expected that lead, with its high atomic weight, would give a dense shadow in vessels so small that only a thin line of the injection mass could enter. A variety of soluble and insoluble lead salts was tested. Many methods of incorporating the lead salt with the agar were tried with varying success. A satisfactory lead-agar mass was finally obtained by dissolving powdered agar in a suspension of freshly precipitated lead phosphate which had never been allowed to dry. This mass was used throughout the series of injections herein reported. To facilitate outlining the distribution of the two coronary arteries, we added methylene blue to the mass injected into the left coronary artery and basic fuchsin to the mass going into the right coronary artery.

Below are given the specific procedures, with their pitfalls indicated, for preparation of the mass, for injection of the arteries, and for unrolling the heart preliminary to making the roentgenogram. After these procedures are carried out, we always perform a complete dissection of the injected arteries in order to confirm, correct, and extend the observations recorded roentgenologically.

TECHNIQUE OF PREPARING HEARTS

Preparation of Tinted Radiopaque Injection Mass

Solution A

Lead Acetate ($\text{Pb}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 3\text{H}_2\text{O}$), C.P.	60.0 gm.
Distilled water	172.0 c.c.

Heat to dissolve; filter through paper; and allow to cool.

Solution B

Disodium phosphate (Na_2HPO_4 , anhydrous) C.P.	24.0 gm.
Distilled water	190.0 c.c.

Heat to dissolve, filter through paper, and allow to cool.

1. Place 1.5 gm. of agar-agar (Difco granular) in a 2,000 c.c. bulb flask.
2. Add 100 c.c. of solution A (lead acetate).
3. Add 1 c.c. of 0.06 per cent phenol red.
4. Add 70 c.c. of solution B (disodium phosphate).

5. Add, from a pipette, 10 per cent NaOH to first permanent pink tinge (about 21 c.c.).
6. Bring total volume to 200 c.c. with distilled water.
7. Boil over free flame with constant stirring until agar dissolves—about ten minutes.
8. Add methylene blue or basic fuchsin in a saturated alcoholic solution—8 c.c.
9. Heat on a free flame for one minute with stirring.
10. Strain, while hot, through several layers of gauze.
11. Distribute into 50 c.c. centrifuge tubes, 35 c.c. to a tube.
12. Stopper and preserve at room temperature.

Final Composition of Injection Mass

Lead (as the insoluble phosphate)-----	8.00%
Agar-agar -----	0.75%
Neutral sodium acetate—phosphate buffer -----	15.00%
Methylene blue or basic fuchsin (in saturated alcoholic solution)--	3.00%

In this mass there is a slight excess of phosphate ion, which insures complete precipitation of the lead. If any soluble lead acetate were present, it would diffuse out of the vessels and produce distortion in the roentgenogram. Attempts to dissolve the agar in the autoclave always resulted in a lumpy mass. The solution over a free flame is carried out in a relatively large flask because at first there is much frothing. As the agar dissolves, the frothing diminishes and finally practically ceases when the solution is complete. If the mass is to be kept in stock for any length of time, it is better to add the dyes after it has been remelted for use, just before injecting it into the arteries. The phosphate mixture is so adjusted that the final reaction of the mass is neutral. This is least injurious to the tissues. The insoluble lead phosphate precipitate falls out of suspension so slowly as not to interfere with the injection procedure.

METHOD OF INJECTING ARTERIES

The coronary arteries are injected as soon as possible after the autopsy. We have injected hearts within an hour or two after death, and after they had been kept in the icebox for several days, and have not noted any consistent difference in the ease or completeness of the injection, or any other variation depending upon the length of this interval. We have never found it necessary to relax the vessels by perfusing them with a solution of potassium sulfocyanide, as suggested by Gross,⁴ when one wishes to hurry the injection. When necessary, the entire procedure can be completed quite rapidly, that is, within one-half hour. We have repeatedly demonstrated the wet roentgenogram and the completely dissected heart at the autopsy table before the remainder of the autopsy was completed. The details of the injection procedure are as follows:

1. Cannulate the right and left coronary arteries.

Dissect carefully around either artery just as it leaves the aorta, and tie the cannula in securely, making sure that no branch is proximal to the tie.

2. Warm heart to 44° C. in a bath of physiologic salt solution.

a. This bath is readily prepared by mixing one part of filtered 18.0 per cent NaCl with 19 parts of warm tap water.

b. A thermometer should be placed directly in the chamber of the left ventricle, as this is the slowest to warm up. This takes from ten to twenty minutes. This bath is easily kept at the proper temperature (44-45° C.) throughout the injection by means of an immersed electric heating coil and a bimetallic immersion thermoregulator.

3. Simultaneously wash both coronary arteries with about 100 c.c. of warm physiologic salt solution injected at 150 mm. Hg pressure.
 - a. The cannulae to the arteries are previously connected to containers (50 c.c. centrifuge tubes) filled with warm physiologic salt solution from the bath. These containers and the rubber tubes connecting them with the cannulae are immersed in the same 44-45° C. bath as the heart.
 - b. Each container is connected to a separate mercury manometer, and, by means of Y-tubes, both to the same 50 c.c. syringe, which is used as a source of pressure.
 - c. Air bubbles are seen to rise from the heart as the warm salt solution fills the vascular system. The salt solution wash should not be discontinued until no more bubbles rise.
4. Simultaneously inject both coronary arteries with the warm lead-agar mass at 150 mm. Hg pressure.
 - a. The mass, kept in 50 c.c. centrifuge tubes, is previously melted in a separate bath of boiling water.

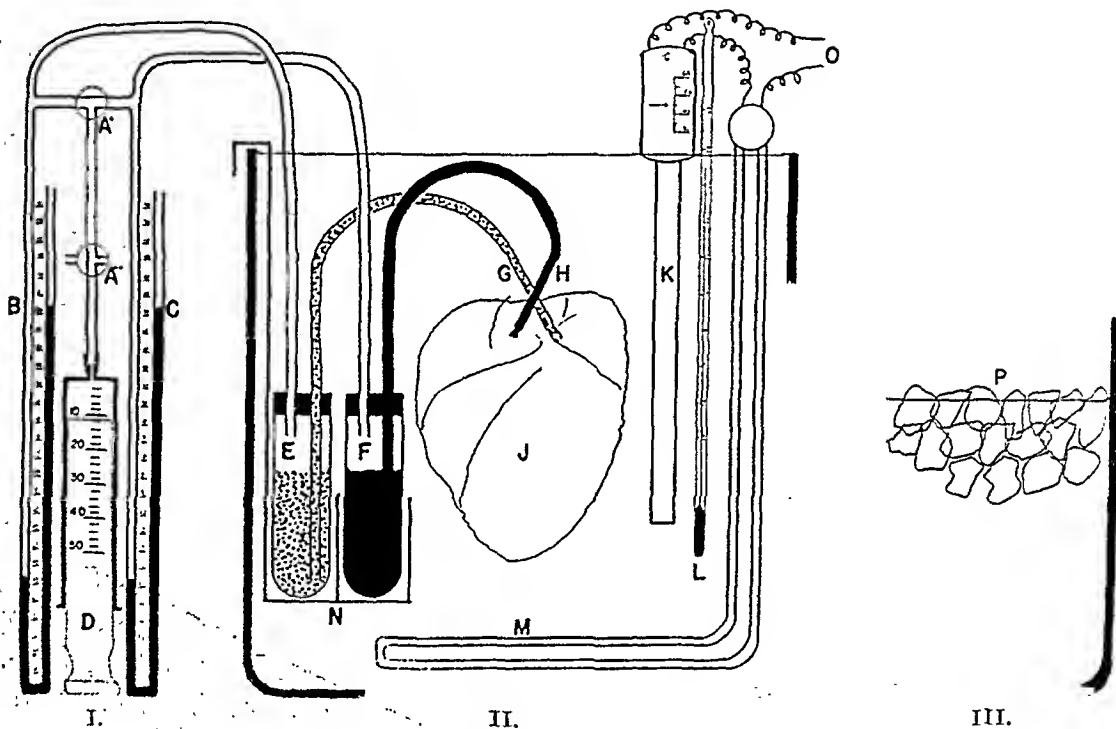


Fig. 2.—Apparatus for injection, composed of:

- | | |
|---|--|
| I. Double manometer consisting of: | |
| A' and A'', three-way stopcocks | C. Manometer for right coronary artery |
| B, Manometer for left coronary artery | D, 50.0 c.c. syringe for pressure. |
| II. 45° C. salt solution bath containing: | |
| E, Reservoir for injection mass for left coronary artery | J, Heart |
| F, Reservoir for injection mass for right coronary artery | K, Thermoregulator |
| G, Cannula in left coronary mouth | L, Thermometer |
| H, Cannula in right coronary mouth | M, Electric Heating Coil |
| | N, Holder for reservoirs |
| | O, To electric outlet. |
| III. Cold salt solution bath with: | |
| | P, Ice. |

- b. The mass after melting is cooled and kept liquid by immersion in the same 44-45° C. bath as the heart.
- c. The injection is continued until the manometer readings remain constant for several minutes at 150 mm. Hg pressure without the application of any more pressure. This usually takes less than five minutes.
5. To insure flow through any anastomoses which may be present, the pressure in the left coronary artery is then reduced to zero or lower, and that in the right

coronary artery kept at 150 mm. Hg. This condition is maintained for several minutes. The process is then reversed, i.e., low pressure maintained in the right coronary artery, and high in the left. (At this stage the heart should be lifted gently from the salt solution for short inspections to be sure that the injection is progressing satisfactorily.)

6. Set the mass by cooling the heart in a separate bath of iced physiologic salt solution.
 - a. The cannulae are previously clamped with the pressure at 150 mm. Hg and the heart disconnected.
 - b. This bath is readily prepared by mixing one part of filtered 18.0 per cent NaCl with ice and sufficient tap water to make a total volume of 20 parts.

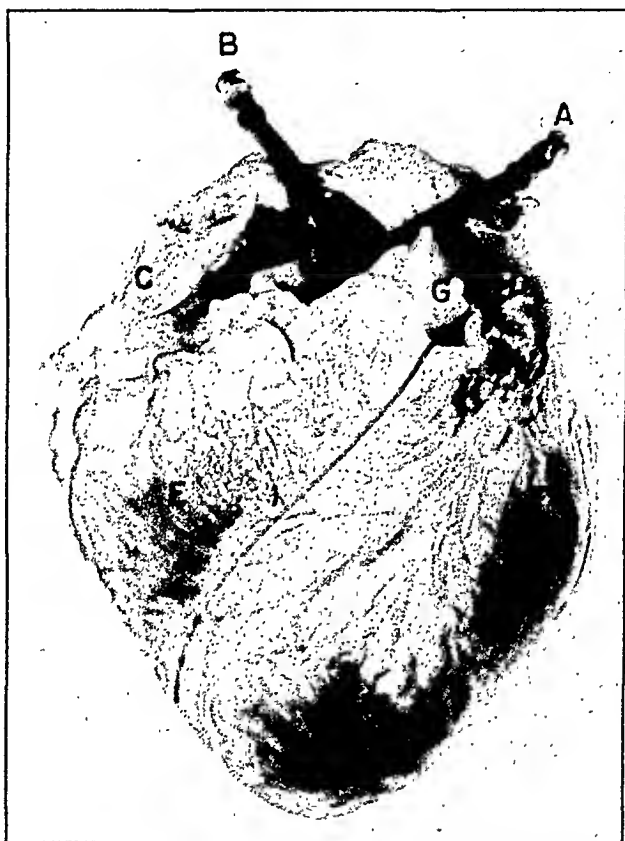


Fig. 3.—Intact heart with incision 1 indicated. (Reduced to $\frac{1}{2}$ normal size.)

In Figs. 3 to 8 the following structures are labelled:

- | | |
|--------------------------------------|----------------------------|
| A, Cannula in right coronary orifice | G, Pulmonary artery |
| B, Cannula in left coronary orifice | H, Interventricular septum |
| C, Right auricle | I, Pulmonary valve |
| D, Left auricle | J, Aortic valve |
| E, Right ventricle | K, Mitral valve |
| F, Left ventricle | L, Tricuspid valve. |

- c. The mass sets quickly at temperatures below 20° C.
- d. The mass will remain solid at room temperature.
7. Dissect the heart to flatten out the coronary arteries (*see* method and steps below).
8. Make roentgenogram of flattened-out coronary arteries.
 - a. Place the heart with the pericardial surface in contact with the x-ray film holder.
 - b. Technical factors used in making radiographs of the unrolled heart:
Tube—XP—1—W; fine focus; distance, 42 inches; milliamperes 20; kilovolts 48; medium cone; time, 1 second; plain folder.

9. Open the coronary arteries as far as possible.

- a. The injection mass will be a gray mush, easily removed in small bits.
- b. The intima of the vessels will be tinted red if reached by the mass from the right coronary cannula, blue if reached by that from the left, and purple if reached by both.

The apparatus for injection is shown in Fig. 2. The entire apparatus is compact, occupying a space 28 inches long and 15 inches wide. It can, if necessary, be constructed from equipment ordinarily at hand.*

INCISIONS AND STEPS NECESSARY TO UNROLL THE HEART AND FLATTEN OUT THE CORONARY ARTERIES

First Incision (Fig. 3). Starting in the pulmonary artery, opening up the pulmonary valve and right ventricle on a line just to the right of the anterior interventricular sulcus, and extending completely to the apex.



Fig. 4.—Incision 1 has been made, and incision 2 is indicated. (Reduced to $\frac{1}{2}$ normal size.)

Second Incision (Fig. 4). Starting in the aorta, between the right and the left anterior cusps of the aortic valve, behind each of which is one of the cannulated coronary artery orifices, extending down about 1 cm. into the base of the septum, and thus dividing again the pulmonary valve and its ring.

*The entire constant temperature apparatus, including thermoregulator, immersion coil, and bath, may be obtained from the American Instrument Company, Baltimore, Md.

The holders for the injection mass were made by Mr. P. Tuzik, 82 Chikatawbut Street, Dorchester, Mass.

The double manometer may be obtained from Macalaster Bicknell Co., of 171 Washington Street, Cambridge, Mass.

Third Incision (Fig. 5). Starting at the inferior termination of the second incision, continuing anteriorly along the base of the interventricular septum to the upper end of the anterior border of this septum, and then along the anterior border of this septum, completely to the apex; thus separating the interventricular septum anteriorly from the ventricles.

Fourth Incision (Fig. 6). Starting again at the inferior termination of the second incision, continuing posteriorly along the base of the interventricular septum to the upper end of its posterior border, and then along the posterior border of this septum, completely to the apex; thus connecting with the third incision and completely removing the interventricular septum.



Fig. 5.—Incisions 1 and 2 have been made, and incision 3 is indicated. (Reduced to $\frac{1}{2}$ normal size.)

Fifth Incision (Fig. 6). Starting at the middle of the free border of the anterior cusp of the mitral valve, this cusp is bisected, and the incision continued through the mitral ring, and through the aortic ring to separate the left aortic cusp from the posterior aortic cusp. The left auricle having been entered from below, the incision is carried parallel to the left side of the interauricular septum to and through the pulmonary veins to unroll completely the left side of the heart.

Sixth Incision (Fig. 7). Starting at the junction of the anterior and the medial cusps of the tricuspid valve, dividing the tricuspid ring and continuing across the aortic ring to separate the right anterior aortic cusp from the posterior aortic cusp. The right auricle having been entered from below, this incision is carried parallel to the right side of the interauricular septum, to and through the superior vena caval opening to completely unroll the heart.* (Fig. 8.)

*The roentgenogram of the vessels of this heart is shown in Fig. 12.

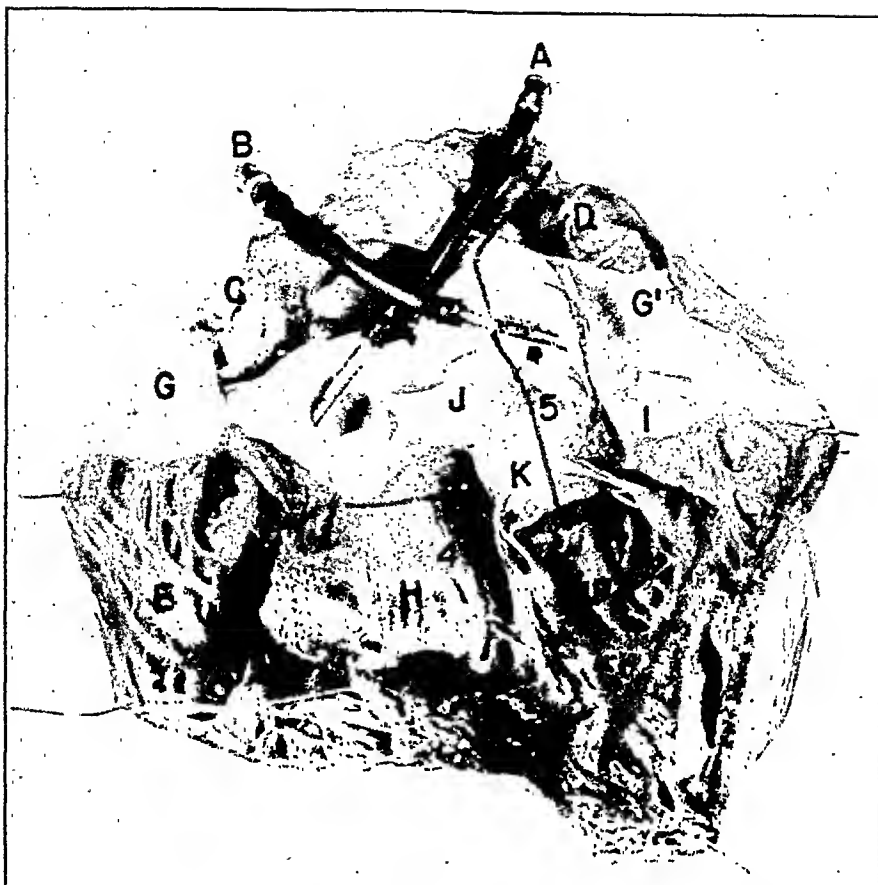


Fig. 6.—Incisions 1, 2, and 3 have been made, and incisions 4 and 5 are indicated. (Reduced to $\frac{1}{2}$ normal size.)

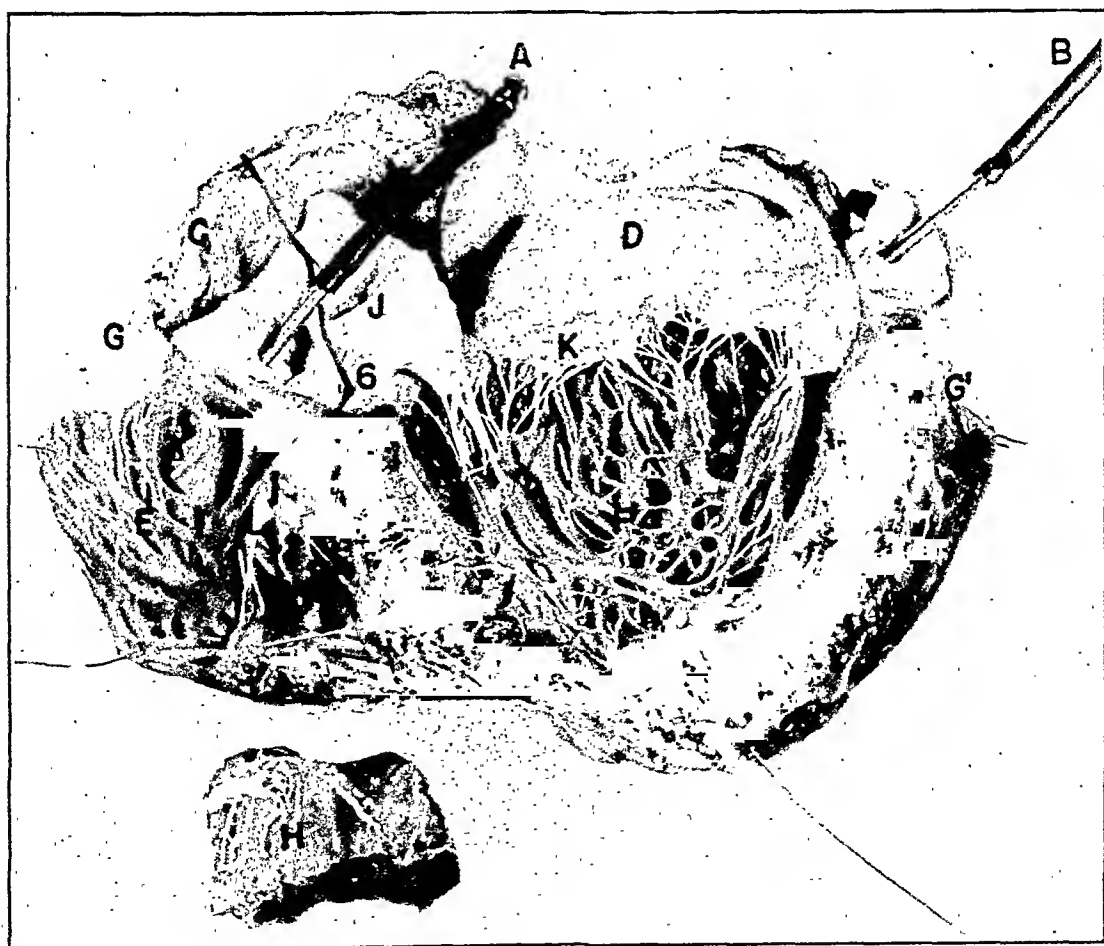


Fig. 7.—Incisions 1, 2, 3, 4, and 5 have been made and incision 6 is indicated. (Reduced to $\frac{1}{2}$ normal size.)

Particular attention is called to incisions 3 and 4, which were devised to remove the interventricular septum. It is often more convenient to make incision 4 before incision 3. The object of these two incisions is to remove completely the interventricular septum from the remainder of the heart. This is accomplished by whatever complicated incisions are found necessary in each particular case, following,



Fig. 8.—Completely unrolled heart viewed from the endocardial surface. (Reduced to $\frac{1}{2}$ normal size.)

however, the landmarks noted above. For these two incisions a small sharp scalpel is most convenient, all the other incisions being made with scissors.

In Fig. 9, from Cunningham,¹⁰ the positions of incisions 1, 2, 5, and 6 are indicated on a diagram of the valves and valve rings of the heart. From this it can be seen that the pulmonary valve is cut in two pieces, and the aortic valve in three segments, by this series of incisions. The auriculoventricular valves are cut across only once. If during the course of the dissection a lesion of the heart which it is undesirable to cut through is encountered, it is always easy to turn aside slightly without altering the general plan significantly.

TECHNIQUE OF STUDYING INJECTED HEARTS

Comparison of Intact and Unrolled Heart

The completeness with which this kind of dissection eliminates the confusing overlapping of arterial shadows obtained by Gross' method is illustrated by comparing Figs. 10 and 11. These pictures were made from the same injected heart* before and after carrying out such a dissection. In Fig. 10, the vessels of the intact heart are viewed as if seen from the back, as in Gross' monograph.⁴ In Fig. 11, the unrolled heart, these vessels are viewed as if seen from the pericardial surface. The picture in this particular heart resembled the Spalteholz diagram so closely that it was possible to label the arteries exactly as they are labeled on that diagram. Only by comparison of the two pictures was it possible

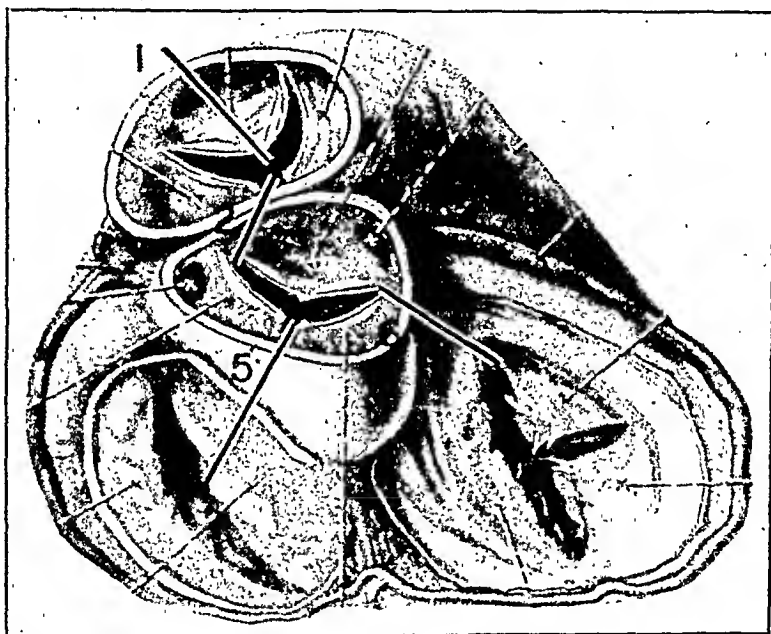


Fig. 9.—Base of ventricles with valves:

- 1, Incision 1 from pericardium to pulmonary valve
- 2, Incision 2 from pulmonary to aortic valve
- 5, Incision 5 from aortic to mitral valve
- 6, Incision 6 from aortic to tricuspid valve.

(From Cunningham's Text-Book of Anatomy, William Wood & Company.)

to label the same vessels in Fig. 10 of the intact heart. Then, to make correlation easier, the key numbers were placed as far as possible in the same relative positions near the appropriate vessels in both figures. Also, the fact that in both figures the branches of the left coronary artery are tinted blue, and the branches of the right coronary artery red aids in the correlation.

Since at no place in the roentgenogram of the dissected heart is the shadow of more than a single thickness of the cardiac wall present, many soft tissue details can also be seen. However, since the injection mass

*This heart (Case 24) was hypertrophied (600 gm.) and was the seat of aortic stenosis with calcification of the aortic ring and leaflets. This calcification is seen in the roentgenogram just above the mouths of the coronaries.

This picture also shows considerable arteriosclerosis of the various arterial branches with some distortion of their lumina and some calcification.

used does not penetrate vessels of the caliber of those going to the valves, this method gives no information about the vascularization of the valves. In pictures such as Fig. 11 each individual vessel can be studied throughout for points of narrowing due to arteriosclerosis. Complete occlusions, of course, are easily seen and localized. The question of anastomosis can also be adequately studied.

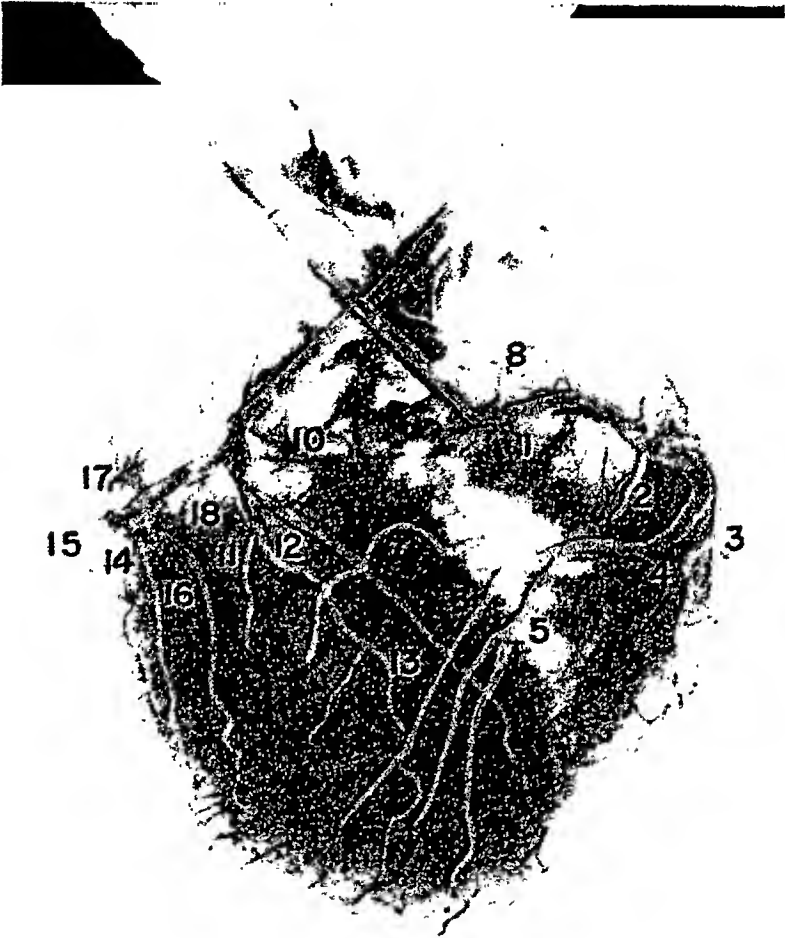


Fig. 10.—Case 24, Intact heart. Numbering of vessels same as in Figs. 1 and 11. (Reduced to $\frac{2}{3}$ normal size.)

Appearances of Arteriosclerotic Narrowing and Occlusion in Injected Vessels

The contour of the shadow of the injected normal arteries is that of a band with smooth walls (Fig. 12). The tapering is uniform. The course of even the most tortuous vessels is easily followed. The occasional overlapping of large vessels causes no confusion. The diameters of each vessel and its branches can be easily measured. Because the exposure is made with the pericardial surface in contact with the film holder, the roentgenogram shows almost no distortion of the diameter of the larger,

more superficial vessels. The diameter of the smaller, penetrating vessels is, if anything, slightly enlarged, making them easier to follow.



Fig. 11.—Case 24. Unrolled heart. Numbering of vessels same as in Figs. 1 and 10. (Reduced to $\frac{3}{8}$ normal size.)

Arteriosclerotic plaques which narrow or distort the lumen are easily seen as irregularities in the contour of the shadow. Not all such plaques cause a narrowing of the lumen. Some cause a distortion of contour without narrowing (Fig. 14). Others cause no distortion whatsoever and are not detected until the arteries are opened up. Stewart, Birchwood,

and Wells,¹¹ using a method similar to that of Gross and injecting at a pressure of 95 mm. Hg, reported that most arteriosclerotic plaques in the coronary arteries cause no narrowing of the lumen. We have repeatedly found irregularities at the sites of arteriosclerotic plaques in the coronaries (Fig. 13, left circumflex artery, and Fig. 16, left descending artery), in spite of the fact that our roentgenograms were taken while maintaining an even higher internal pressure (150 mm. Hg). This discrepancy is probably due to the fact that unrolling the heart produces a sharper, less distorted view of the injected vessels and brings out details better.

Calcified plaques present a picture interesting in its variations. If the radiopacity of the plaque is the same as that of the injection mass, the shadow of the plaque may fuse with that of the column representing the lumen, or may appear as an outpocketing of this lumen (Fig. 14, left descending artery.) When the lead-agar and the calcified plaque are of different densities, the plaque often stands out quite distinctly (Fig. 15, right coronary artery.) Interesting pictures are obtained when a row of small plaques in the wall of the artery are separated from the lumen by a noncalcified layer. Then the shadow of the lead-agar in the lumen has a wavy irregular contour, next to which, and parallel to which, is a series of irregular opaque blotches representing the calcified plaques (Fig. 13, right coronary artery.)

Zones of complete occlusion usually appear as obvious defects in the shadow of the injected lumen. However, if the occluded zone is calcified, the shadow of this calcium may simulate injection mass in the lumen. No final decision as to the patency or occlusion of any vessel can be made from the roentgenogram alone. This decision is always reserved until after the coronary arteries have been dissected.

Anastomotic Zones Between Right and Left Coronary Arteries

In the roentgenogram of the unrolled heart the possible anastomotic zones between the right and left coronary arteries are all widely separated, whereas in that of the intact heart these zones directly overlie one another. The first of these zones lies in the anterior portion of the right ventricle just to the right of, and parallel to, the anterior interventricular groove. The first incision described above is made near this zone. Along this line are the terminal twigs of many of the branches of the right coronary artery, and also such branches of the left descending coronary artery as may go to the right ventricle. These vessels are quite obvious before dissection because the branches of the right and left coronary arteries are injected with masses of different colors. One can avoid going directly through this zone by placing the incision properly. In Fig. 11, along the cut edge of the heart, parallel to the left descending coronary artery, several terminal twigs of the right coronary artery may be seen. If there were any injected anastomotic vessels bridging this gap, their shadows would be perfectly obvious.

The second possible zone of anastomosis between the right and left coronary arteries lies in the region of the posterior interventricular groove. According to Spalteholz,⁵ in 80 per cent of human hearts the posterior descending artery, lying in this groove, is the terminal portion of the right coronary artery. This is exemplified by the heart shown in Fig. 11. Ordinarily branches, or at least terminal twigs, from both the left circumflex coronary artery and the left descending artery reach this groove. We have found, as have Spalteholz,⁵ Whitten,¹² and others, that the commonest variations in the vascular supply of the heart are found in this zone. These variations are especially easy to study in the roentgenograms of the unrolled heart and will be the subject of a separate communication. It is in this region that deceptive shadows of seemingly anastomotic channels are most often encountered in the roentgenograms; individual branches of fair caliber often appear to bridge this gap between the left and the right coronary arteries. On dissection, however, these vessels are found to lie in different planes.

In both Saphir's modification¹ of Spalteholz's diagram and a drawing in *Cunningham's Textbook of Anatomy* (Fig. 9), a large artery is shown as a normal anastomotic channel between the termination of the left circumflex coronary artery and the right coronary artery. Mautz and Gregg¹³ experimentally induced the formation of a large anastomotic channel in this location in a dog by tying off the right coronary artery. In the human heart we have only once (Case 34, Table I) found such a channel. Our dissections have convinced us that in man such roentgenographic appearances should be considered as artifacts unless their existence is confirmed by dissection.

The interventricular septum provides the third possible zone of anastomosis between the right and the left coronary arteries. One or more large branches of the left descending coronary artery regularly penetrate this structure. It also ordinarily receives a larger number of smaller branches from its posterior border. These branches of posterior origin vary in their source, depending upon which vessels traverse the posterior interventricular groove. These may be branches either of the right or left coronary artery, or both. After injecting the heart and before making the roentgenogram, we remove this septum and turn it so that its left ventricular surface is in contact with the x-ray folder, thus avoiding overlapping of vessels. Fig. 11 not only shows the stump of the septal arteries, as in Spalteholz's diagram, but also their complete distribution in the body of the septum. This is even better shown in Figs. 12 and 16.

Method of Proving the Presence of Anastomoses

A final decision as to the presence or absence of an anastomosis would often be impossible if we had to depend upon the roentgenogram alone, or even upon the roentgenogram and ordinary dissection. The use of dyes of different colors in the masses used to inject the right and left.

coronary arteries is all-important. When the injection, roentgenogram, and dissection of the vessels are completed, the distribution of these dyes enables one to say with certainty from which coronary opening a particular vessel was injected. Three types of anastomoses are then recognizable.

The anastomotic channels may carry the blood from one large branch of one of the two coronary arteries to another large branch of the same vessel, or serve to bridge a gap in one of the branches of the vessel. We have called these left to left (L to L), or right to right (R to R) anastomoses. An obvious R to R (or L to L) anastomosis is present when there is a definitely occluded zone in the lumen of one of the coronary branches, and the distal part of this branch is fully injected with mass of the same color as that found proximal to the zone of occlusion. This is the commonest type of anastomosis (Fig. 16). In the absence of a point of occlusion with injection beyond, all the precautions enumerated will not exclude the presence of functional anastomotic channels between branches of the same coronary artery. Since the procedure used yields adequate objective evidence of all other types of anastomoses, this might have proved a serious defect of the method. However, anastomoses of this kind were detected by tying off one or more of the smaller arterial branches just before injection (Fig. 13). The injected mass was thus prevented from penetrating beyond the artificial occlusion except via anastomotic channels. This special procedure is not necessary in every case but was employed often enough to rule out the possibility that anastomoses of this kind occur in normal hearts.

There is a second type of anastomosis, in which, proximal to a completely occluded point, is found mass of one color filling the vessel and its branches, whereas distal to the occlusion, in what is obviously the continuation of the same vessel, is found mass of the opposite color. We have called these left to right (L to R) or right to left (R to L) anastomoses. Under such circumstances, it is obvious that a portion of the myocardium and of the vessels supplying it have become entirely dependent upon the opposite coronary artery for their blood supply (Fig. 14).

A third form of anastomosis is that in which one or more arterial branches receive blood from both coronary arteries. A vessel which receives blue mass from the left coronary artery, and red from the right, necessarily stains purple (Fig. 15), and we have called this a convergent anastomosis. On rare occasions all the branches of both coronary arteries are tinted purple of varying shades. More often a few branches distal to their occluded zones become purple, whereas other similarly occluded branches are filled with either pure red or pure blue mass.

ANALYSIS OF RESULTS

Fifty-six human hearts have been injected and studied by a uniform technique similar to that described above. In ten of these the injection was imperfect because of technical difficulties. The commonest sources

of error were the use of a salt solution immersion bath which was too cool, or of a leaky or plugged pressure system. Of the remaining 46 hearts, 8 were from patients less than 50 years of age. Inasmuch as we wished to clarify the relationship between anastomoses and occlu-

TABLE I
COMPLETE DATA ON ALL HEARTS INJECTED

CASE NO.	AGE (YR.)	DEGREE OF CORONARY ARTERIO-SCLEROSIS	ARTERY OCCLUDED	TYPE OF ANASTOMOSIS	IN-FARCT	DEGREE OF HYPER-TENSIVE HYPER-TROPHY	VALVE WITH LESION
1	73	++	R	L to R		+++	AV
2	58	+	R	L to R		++	
3	57	+		Con.		+	
4	64	0					
5	61	+++	LD, LC, R	L to R; L to L			
6	52	+					
7	51	0		Con.			MV
8	72	0					AV
9	62	++	LD	L to L			
10	72	+					
11	53	+++	LD, LC, R	L to L; R to R; L to R; R to L; Con.	*		
12	67	++					
13	62	+					
14	72	0					
15	78	+		R to L			AV, TV, MV
16	76	++					
17	66	+++	LD, LC, R	L to L; L to R		+++	
18	69	+++	LC, R	L to L; L to R; R to R	*		
19	51	+	LC	L to L	*		
20	56	0					
21	62	0					
22	62	+++	LD	Con.	*		
23	65	++	R	L to R; R to L			MV
24	80	+++					AV
25	56	+					
26	58	0					
27	80	++	LC	Con.		++	
28	65	0					AV
29	67	0					
30	63	+					
31	66	+++	LD	L to L			
32	63	+				+	
33	72	+					
34	70	+++	LC, R	L to L; L to R	*		
35	75	+++	R	L to R			
36	63	0					
37	72	+				++	MV
38	55	+++	LD, LC, R	L to L; R to R; Con.	*		

Arteriosclerosis: 0, none; +, slight; ++, moderate, +++, marked.

Artery occluded: LD, left descending coronary artery or its branches; LC, left circumflex coronary artery or its branches; R, right coronary artery or its branches.

Type of Anastomosis: L to L, anastomosis between branches of the left coronary artery; R to R, anastomosis between branches of right coronary artery; L to R, branches of the right coronary artery entirely supplied from the left coronary artery; R to L, branches of the left coronary artery entirely supplied from the right coronary artery; Con., branches of one or both coronary arteries supplied by a mixture of blood from both coronary arteries.

Valvular lesion: TV, tricuspid valve; MV, mitral valve; AV, aortic valve.

sions of the coronary arteries, these 8 hearts were purposely omitted, for, according to previous workers in this field, anastomoses are likely not to be well established before the age of 50 years.

The data on these 38 hearts are shown in Table I. Seven (Cases 4, 14, 20, 21, 26, 29, and 36) were essentially normal, and 8 (Cases 6, 10, 12, 13, 16, 25, 30, 33) showed only minimal or moderate degrees of atheromatosis of the coronaries. No anastomoses were present in any of these fifteen hearts. The remaining 23 hearts were definitely pathologic. The lesions, although quite varied, consisted principally of (1) marked arteriosclerosis with or without complete occlusion of coronary artery branches, (2) valvular lesions of various types, and (3) hypertensive hypertrophy; some of the hearts displayed various combinations of these three kinds of abnormalities. Three hearts (Cases 3, 7, 15), although from patients over 50 years old, were also purposely omitted from further consideration at this time. In these three hearts anastomoses without occluded vessels were present. They showed hypertensive hypertrophy, rheumatic mitral stenosis, and subacute bacterial endocarditis respectively. The above omissions reduce the number of hearts under discussion to 35.

In Table II, these 35 hearts are grouped according to age and the presence or absence of anastomoses in the coronary artery tree, and we see that there is a complete lack of correlation between the two. In both groups, with and without anastomoses, over 80 per cent of the hearts were from persons over 60 years of age. Nevertheless, in 57 per cent of

TABLE II
AGE INCIDENCE OF CORONARY ARTERY ANASTOMOSES

	AGE IN DECADES			TOTAL
	50-59 YR.	60-69 YR.	70-80 YR.	
No anastomoses	4	9	7	20
Anastomoses	4	7	4	15

the hearts no coronary artery anastomoses were demonstrable by a standard technique which readily visualized such anastomoses in the remainder. In all 15 hearts in which anastomoses were found, there were also one or more occluded coronary artery branches. No occluded branches were found in the other 20 hearts without anastomoses. Thus it would appear that coronary artery anastomoses are related less to advancing age than to the necessities which arise as a result of occlusion of coronary artery

TABLE III
ARTERIOSCLEROSIS AND CORONARY ARTERY ANASTOMOSES

	DEGREE OF ARTERIOSCLEROSIS				TOTAL
	NONE	SLIGHT	MODERATE	MARKED	
No anastomoses	9	8	2	1	20
Anastomoses	0	2	4	9	15

branches. The occlusions themselves are, of course, in practically all instances, a sequence of arteriosclerosis, and there is in general a definite increase in arteriosclerosis of the coronary arteries with increase in age, but many individual variations are encountered. In a given heart, the more extensive the arteriosclerosis, the greater the probability that coronary artery occlusion will occur. Therefore, there should be a direct correlation between the incidence of anastomoses and the amount of coronary arteriosclerosis. In Table III the hearts are grouped according to the degree of arteriosclerosis and the presence or absence of anastomoses. In preparing these data the amount of arteriosclerosis in the coronary arteries was estimated in four degrees of intensity, namely, none, slight, moderate, and marked. In arriving at this estimate, both the roentgenogram and observations on the dissected coronaries were utilized. In 85 per cent of the hearts that showed no coronary artery anastomoses, there was less than a moderate degree of coronary arteriosclerosis. Of the hearts in which there were coronary artery anastomoses, 80 per cent showed moderate to marked arteriosclerosis.

For the 15 hearts in which there were completely occluded coronary artery branches Table IV summarizes the data as to the sites of the occlusions, the types of anastomoses, and the presence of infarcts. Adequate statistical study of the interrelation of these factors will have to await a larger series. A few significant observations can, however, be made. In the 25 occluded coronary artery branches in these 15 hearts, there is a higher incidence of occlusion of the right coronary artery, or its branches, than of either of the main divisions of the left coronary artery or their branches. Moritz and Beck¹⁴ also found a high incidence of right coronary artery occlusions after the age of 60 years.

TABLE IV
RELATION OF OCCLUDED VESSEL TO ANASTOMOSES PRODUCED

CASE NO.	OCCLUDED VESSEL			INFARCT	NATURE OF ANASTOMOSES				
	LD	LC	R		L TO L	R TO R	L TO R	R TO L	CON- VERGENT
1			*				*		
2			*				*		
5	*	*	*		*		*		
9	*		*		*		*	*	*
11	*	*	*	*	*	*	*		*
17	*	*	*	*	*	*	*		
18		*	*	*	*	*	*		
19		*		*	*				
22	*			*			*	*	*
23			*				*	*	*
27		*					*		
31	*		*		*		*		
34		*	*	*	*		*		
35			*	*	*		*		
38	*	*	*	*	*	*			*
Totals	7	8	10	6	9	3	9	2	4

Abbreviations as in Table I.

In six (Cases 5, 11, 17, 18, 34, 38) of these fifteen hearts there were complete occlusions in branches of more than one of the three major divisions of the coronary arteries. Because of the fairly common occurrence of multiple points of occlusion, impressions of the incidence of occlusions are valueless unless based on a method permitting complete study of all the coronary artery branches in every heart. In four (Cases 11, 18, 34, 38) of these six hearts with multiple complete occlusion, there were either fresh or healed infarcts. However, two infarcts, one fresh and one healed, were also present in each of two other hearts (Cases 19 and 22) in which there was only one completely occluded branch. Thus, with more extensive arteriosclerosis and a large number of vessels affected, the probability of infarction was greater. Infarction, however, may occur in a heart with very little arteriosclerosis and with only one major vessel completely occluded (Case 19).

Analysis of the paths of the anastomotic circulation following complete occlusions brings out the point that in only three hearts (Cases 9, 19, 31) was the compensatory anastomotic circulation entirely dependent upon connection with the coronary artery whose branch was occluded. In all other instances there was an anastomotic channel established with the opposite coronary artery. As a result of this new pathway the branches distal to the occlusion were then either fed entirely from the opposite coronary artery, or were supplied with a mixture of blood from both coronary arteries. In only two instances (Cases 11 and 23) was an occluded branch of the left coronary artery thereafter fed entirely from the right coronary artery. Also, it was unusual for an occluded branch of the right coronary artery to receive its blood supply entirely from that artery after the occlusion occurred. There were only three examples (Cases 11, 18, and 38) of this type of readjustment of the circulation. In nine hearts (Cases 1, 2, 5, 11, 17, 18, 23, 34, 35), however, the left coronary artery had served as the source of supply for an occluded branch of the right coronary artery. It should be noted that in Case 11 examples of all three of these types of anastomoses were found. This heart, however, presented a very complicated anastomotic circulation (Fig. 15). In general, it can be said that blood from the left coronary artery usually reaches whatever branches of either coronary artery which are deprived of their original source of supply. Sometimes this anastomosis from the left coronary artery furnishes the whole supply, but there is often an intermingling with blood coming by anastomotic channels through the right coronary artery.

ILLUSTRATIVE CASES

Almost without exception, the roentgenograms of each of the 56 hearts thus far injected were worthy of individual study and threw light on one or more points in cardiac anatomy or pathology. This was especially true of the injected arteries, but the unrolled heart also gave such a



Fig. 12.—Case 32. Normal heart. (Reduced to % normal size.)

- A, Interventricular septum
 B, Left auricular appendage
 C, Right auricular appendage
 D, Left anterior papillary muscle (divided in 2 parts)
 E, Left posterior papillary muscle
 F, Columnar carinae
 G, Conus arteriosus
 H, Anterior edge of interventricular septum
 I, Posterior edge of interventricular septum
 J, Interventricular septum
 K, Apex of heart
 L, Obtuse border of heart
 M, Acute border of heart.

satisfactory soft tissue shadow on the roentgenogram that most of the various intracardiac structures could be identified, studied, measured, and many of their abnormalities recognized. We are reproducing the roentgenograms of only five of our forty-six successfully injected hearts. These five hearts have been selected to illustrate the possibilities of the study of cardiac vascular disease by this method. Only a brief discussion of the clinical history of each patient will be given. The complete correlation, as far as possible, of the pathologic and the clinical data for the entire series will be the subject of a separate communication.

CASE 32.—Fig. 12. Normal heart.

Clinical History.—A man, 63 years old, was operated on for an incarcerated inguinal hernia. Four months later, he developed signs of intestinal obstruction. Laparotomy and ileostomy were performed. He developed postoperative atelectasis, bronchopneumonia, and pulmonary embolism, and died thirteen days after the operation. He had never had any cardiac signs or symptoms.

Heart.—The heart weighed 420 gm. There were no valvular or other lesions, except a slight hypertrophy of the left ventricle, probably hypertensive in origin.

Coronary Arteries.—The coronary arteries showed only small scattered arteriosclerotic plaques, but no narrowings or occlusions, and no anastomoses. Their pattern with one exception was the same as that reported by Spalteholz in 80 per cent of human hearts. The exception was that the terminal branch of the left descending coronary artery turned back on the anterior surface of the heart. Ordinarily, when this branch extends beyond the apex, its termination is found on the posterior surface of the heart. The counterparts of the various anatomic landmarks labeled on this roentgenogram can be recognized easily on all the others. The various arterial branches are similar to those labeled in Fig. 11.

CASE 5.—Fig. 13. Angina pectoris, hypertension, arteriosclerotic heart disease.

Clinical History.—A woman, 60 years old, had suffered for two years before the first admission from dyspnea, palpitation, and substernal squeezing pain which radiated to the left shoulder. These symptoms occurred about once a month, and were relieved by rest. Examination revealed only an enlarged heart, and a blood pressure of 210/120. After total ablation of the thyroid the blood pressure dropped to 140/80, and the electrocardiogram showed normal rhythm, rate 95, low T_1 , and inverted T_2 and T_3 of the coronary type. There were no anginal attacks and no dyspnea for nineteen months after the operation. After this, there were repeated anginal attacks which became increasingly severe and numerous. Death occurred thirty-four months after the thyroidectomy.

Heart.—The heart weighed 510 gm. There were no valvular lesions. The left ventricle was definitely hypertrophied. There were no infarcts. The myocardium showed no fibrosis grossly or microscopically.

Coronary Arteries.—The coronary arteries showed marked arteriosclerosis which was confined to relatively limited zones in the larger branches. From the roentgenogram alone it appears that the greater part of the left descending coronary artery is missing. The distal portion of this vessel with its wider lumen is well shown. Dissection revealed that in the apparently missing segment of this vessel there was so much arteriosclerosis (without calcification) that the vessel had been converted into a cord with a narrow, tortuous lumen. This lumen was discontinuous. On the roentgenogram is seen a brush of neighboring vessels which probably served as anastomotic channels. In none of them could a communication be traced between the proximal and distal end of the occluded artery. Many of these vessels are in the interventricular septum, for in this injected heart the septum was not removed before the roentgenogram was made.



Fig. 13.—Case 5. (Illustration reduced to 3% normal size.)

A, Fresh thrombus

B, Calcified plaque

C, D, Narrowed branches (arteriosclerosis)

E, Narrowed lumen; calcified wall

F, Occluded lumen

G, Anastomatic injection

H, Artifact

In the left circumflex coronary artery a different mechanism for occlusion is illustrated. There is much less arteriosclerosis in this vessel. The marked narrowing of the mouths of two of its main branches is well shown at *C* and *D*. Also, a calcified plaque is shown at *B*. Proximal to this plaque is found a zone, *A*, of complete occlusion by a freshly deposited thrombus. However, distal to this completely occluded zone, the remainder of this vessel was well injected with blue mass from the left coronary artery. Thus the whole left coronary system was well injected in spite of occlusion of its two main stems near their origins.

The whole right coronary system was likewise injected from the left coronary artery. No red mass in the right cannula flowed into any of the vessels. The main stem of the right coronary artery was completely occluded just at its origin, *F*. For a considerable distance distal to this point of complete occlusion there was marked narrowing of the lumen with calcification in the walls. This lumen shown at *E* was dissected open and found filled with the blue mass from the left cannula.

A point of special interest is the branch of the right coronary artery, marked *G*. It arose very close to the origin of this artery, and the right cannula was accidentally inserted distal to its origin. This vessel, nevertheless, was well filled with blue mass through an anastomosis from the left side. The shadow of an uninjected proximal portion extending almost up to the cannula can also be made out. Presumably, in the living heart, this vessel was the only branch capable of receiving blood through the right coronary orifice. If it had not been tied off before the injection, an altogether different pattern of anastomoses might have been found.

The irregularly shaped radiopaque area at *H* represents what would have been a hematoma in life. This heart was rather roughly handled during the injection procedure and the pericardium at this area was bruised. A few small branches must have been ruptured, for the mass leaked into the subepicardial tissues.

Comment.—The anastomotic circulation in this heart was so rich that it permitted an adequate injection throughout the heart in spite of the fact that both main branches of the left coronary artery and the main stem and a main branch of the right coronary artery were occluded at the time of injection. This anastomotic circulation was developing during the five years when the patient was having angina. Possibly the thyroidectomy prolonged the patient's life and thus afforded time for the rich anastomotic circulation to develop. This anastomotic circulation was so efficient that there was practically no fibrosis of the myocardium. Unquestionably, the final fatal insult to the heart was the deposition of the thrombus in the left circumflex artery, but because adequate anastomoses had developed in advance, no infarct resulted, and the patient died of cardiac failure.

A similar sudden occlusion without infarction probably could have occurred in the branch of the right coronary artery which was tied off from the cannula, since this vessel was likewise well injected from the left coronary artery. Judging from its wide-open connection with the right coronary artery, it can be assumed that the flow into this vessel in the living heart was largely from the right coronary artery, for the pressure gradient, in the sense of Wiggers,¹⁵ must have been higher in this direction.

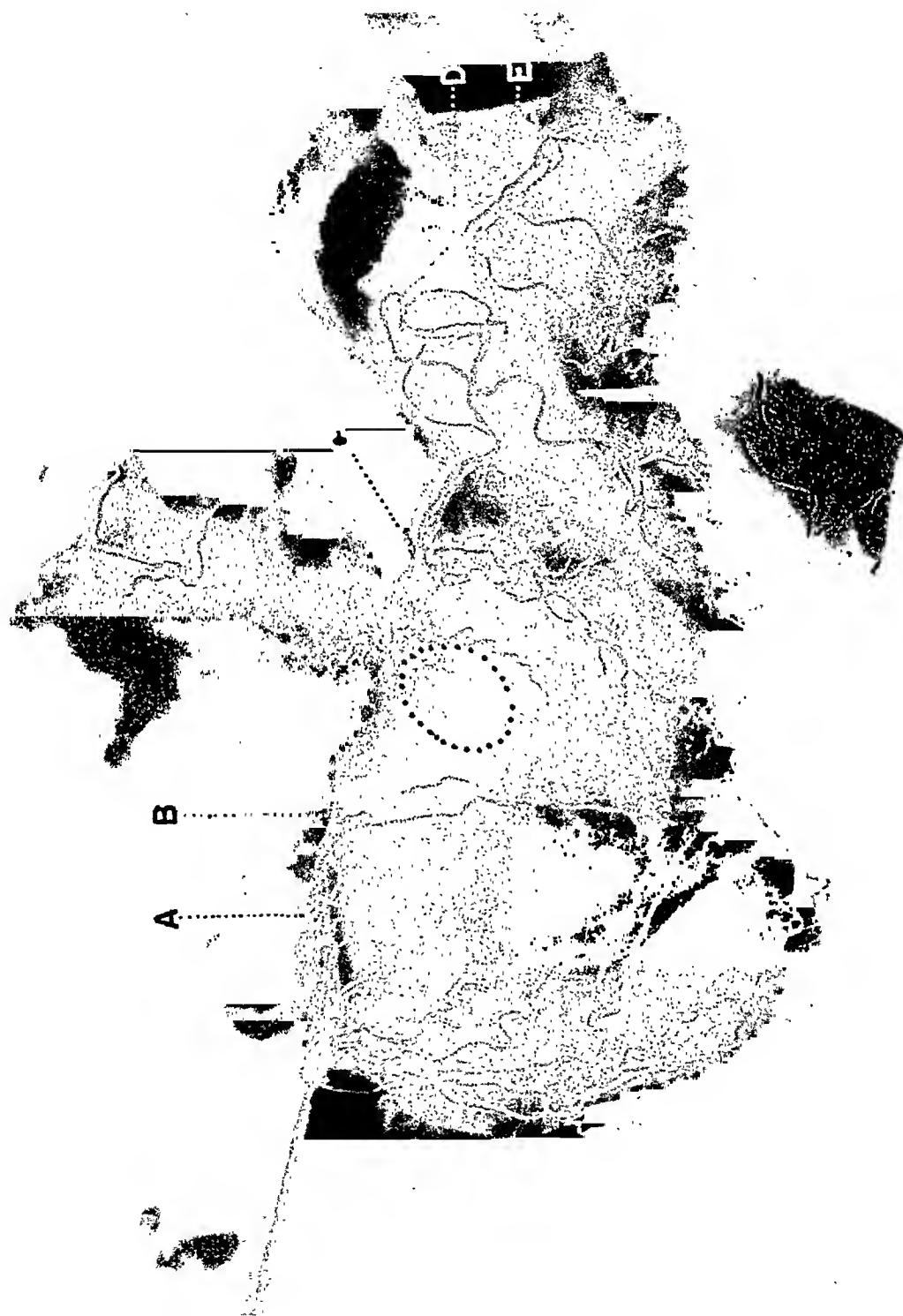


Fig. 14.—Case 18. (Illustration reduced to $\frac{2}{3}$ normal size.)
A, D, E, Nonoccluding thrombus B, Occluding thrombus C, Old occlusion (arteriosclerosis).

CASE 18.—Fig. 14. Angina pectoris, mild hypertension, arteriosclerotic heart disease, mild congestive failure.

Clinical History.—The patient was a man, 69 years of age, who for two and a half years had had precordial pain brought on by exertion and accompanied by dyspnea and palpitation; he had lost a little weight, and complained of epigastric distress and anorexia. The first admission was one year ago for mild congestive failure. Examination at that time showed slight cyanosis, moderate enlargement of the heart, reduplication of the first sound at the apex, accentuation of the aortic second sound, and diminution in the intensity of the pulmonic second sound. The blood pressure was 180/110. The electrocardiogram showed normal rhythm, a rate of 80, left axis deviation, wide and notched QRS waves in all leads with intraventricular block, low T-waves in all leads. Another electrocardiogram two weeks later showed sinoauricular bradycardia, a rate of 48, and a diphasic T-wave. After digitalization and venesection, the patient was advised to take 0.1 gm. of digitalis daily, and was discharged. He was reasonably well for a year except for occasional attacks of precordial pain. These became more severe and more frequent about one month before admission, and were only partially, or not at all, relieved by nitroglycerin. The second admission was on account of a sudden large hematemesis which was probably due to the chronic gastric ulcer found at autopsy. In spite of transfusions and other treatment, he died on the fourth day.

Heart.—The heart weighed 380 gm. There were no valvular lesions. Microscopically the myocardium showed diffuse fibrosis. There was a small, old, healed infarct in the posterior wall of the left ventricle near the auriculoventricular groove. Its outline is indicated on Fig. 14 by the dotted line. There were no fresh or recent infarcts.

Coronary Arteries.—The coronary arteries showed marked arteriosclerosis with calcification and narrowing, but in most cases without occlusion. In the roentgenogram this arteriosclerosis is betrayed by the marked irregularity of the contour of all the large vessels. Several fresh stringy ante-mortem thrombi were present in these narrowed vessels. These had obviously been deposited just before death. In the roentgenogram their locations in the left circumflex and right coronary arteries are indicated by the letters *A*, *B*, *D*, and *E*. Neither thrombus in the right coronary artery, *D* and *E*, was large enough to cause complete obstruction. This was likewise true of the thrombus located at *A* in the left circumflex artery. However, the second thrombus, located farther along in this vessel, at *B*, had caused complete occlusion, and the vessel distal to this fresh occlusion was not injected. The shadow of the noninjected vessel beyond this occluding thrombus is plainly outlined, however, by the faint line of calcification in its walls.

A point of special interest is the terminal branch of the right coronary artery. In the roentgenogram this appears to be well injected, and not especially unusual. When dissected out, it was found to be entirely injected with blue mass from the left coronary artery instead of with red mass from the right coronary artery. The dissection disclosed a sharp, definite point of complete occlusion separating this terminal branch from the right coronary artery. This zone of complete occlusion was only about two millimeters long and is indicated at *C* in the roentgenogram. The anastomoses connecting this terminal branch of the right coronary artery with the left coronary artery were not traceable by dissection. Nevertheless, the roentgenogram shows several vessels which appear to bridge this gap.

Comment.—The roentgenogram of this heart well illustrates the varying pictures obtained in an extreme degree of widespread, marked coronary arteriosclerosis with calcification. Although this arteriosclerosis had gone on slowly to complete occlusion in the right coronary artery,



Fig. 15.—Case 11. (Illustration reduced to $\frac{2}{3}$ normal size.)
A, B, C, D, E, F, I, K, Old arteriosclerotic occlusions with anastomotic injections
G, H, Embolic occlusions
J, Thrombotic occlusion.

such an efficient anastomotic circulation had been established that the small cardiac infarct which formed healed completely without presenting any signs or symptoms of acute coronary occlusion. However, there is little evidence for anastomoses elsewhere in this heart, for, when the termination of the left coronary was suddenly occluded by a thrombus, its distal portion remained uninjected.

CASE 11. Fig. 15. Severe angina pectoris, arteriosclerotic heart disease, multiple coronary artery occlusions with rich anastomoses, terminal thrombosis and coronary embolism.

Clinical History.—The patient was a man, 53 years old, who had had syphilis twenty years before and had recovered under treatment. For ten years he had suffered from pain in the precordium which was brought on by exertion and was relieved by rest. For three years the pain had been substernal and severe, radiating down the left arm, brought on by excitement or exertion, and relieved by nitroglycerin and rest. The attacks had been increasing in severity and frequency for two weeks. Twenty-two hours before death there occurred a more severe squeezing type of precordial and substernal pain, not relieved by nitroglycerin. Physical examination showed little except a gross irregularity of the heart and a pulse deficit. Three hours before death he had another attack of substernal pain and became cold and clammy. The blood pressure could not be measured, the pulse became imperceptible, and the heart sounds were very faint. It was thought that his heart had ruptured. He died three hours later.

Heart.—The heart weighed 350 gm. There were no valvular lesions and no rupture. The myocardium showed diffuse fibrosis throughout, and in the left ventricle there was one small area of marked thinning with almost complete replacement by fibrous tissue. This appeared to be a small, healed infarct. It is outlined by the dotted line in Fig. 15.

Coronary Arteries.—The coronary arteries showed marked arteriosclerosis which in numerous branches had gone on to complete occlusion and obliteration of the lumen for as much as 2 cm. at a stretch. Some of these are indicated in the roentgenogram at the points marked *A, B, C, D, E, F, I, and K*. In the left coronary artery such areas of complete occlusion (*C* and *E*) had broken the continuity of both the circumflex and the descending branches close to their origins. Nevertheless, both branches distal to the occluded zone were open and well injected, but the injection mass reached them by anastomotic channels from different sources. The left circumflex artery still received blood entirely from the left coronary artery as indicated by its content of pure blue mass. The left descending artery, however, was entirely filled from the right coronary artery with red mass. One of its branches, *A*, also entirely cut off from the main artery, was still receiving all its blood supply through an anastomosis with the stump of the left coronary artery. Another branch, *B*, less completely isolated, was receiving blood from both coronaries, as indicated by its content of purple mass.

The branch of the left descending coronary artery marked *D* deserves special consideration. In the roentgenogram, for a distance of 1 cm. from its origin it appears to be poorly injected and shows an irregular contour. Distal to this zone it appears to be well injected. When we attempted to open this vessel, no lumen was found up to a point just proximal to its bifurcation. The entire proximal part was a solid calcified cord. This calcified cord appears in the roentgenogram as if it were patent and completely injected with the radiopaque mass. This illustrates another of the pitfalls which are encountered when the coronary circulation is studied by any method, whether corrosion, clearing, or x-ray, which does not also include a thorough dissection of the vessels as part of its routine.

In the right coronary artery, the lumina of many of the major branches (*F*, *I*, and *K*) were separated from the lumen of the main stem. These branches are all well injected, however, one from the right coronary artery, one entirely from the left, and one from both coronary arteries. In the roentgenogram in some places (*F* and *I*) there appear to be quite large, newly formed, bridging, anastomotic channels. None of these could be dissected out to show actual continuity of the lumen.

In the main stem of the right coronary artery near its origin, at *J*, there was a large atheromatous ulcer with a freshly deposited, soft, ante-mortem thrombus adherent to it. This thrombus had caused practically complete occlusion at this point. At two points (*H* and *G*) farther along in this same vessel, there were loosely attached blood clots which completely occluded the lumen. These were found in portions of the vessel which were somewhat narrowed by atheromatous patches, but without any ulceration present. They were interpreted as emboli which had broken loose from point *J*.

Comment.—In this heart, in spite of multiple points of complete coronary artery occlusion, there was only one small, old, healed area of infarction. In the ten years during which the patient had had repeated anginal attacks, a new and very complicated anastomatic circulation had been set up. The numerous lesions of the coronary branches must have progressed so slowly to complete occlusion that sufficient time was afforded, in all instances, for the development of adequate anastomoses.

The special features of the terminal episodes are also reflected in the heart. The severe attack which brought the patient to the hospital was probably coincident with the deposition of the thrombus on the atheromatous ulcer near the origin of the right coronary artery. Although this had occurred twenty-two hours before death, there was no indication of the beginning of an infarct in the area supplied by this vessel, and no large area of the myocardium was avascular. Thus, in a heart with such a rich anastomotic circulation, the sudden occlusion of even a large vessel may not result in an infarct. Probably such sequences had occurred at numerous times during the preceding ten years. It is also probable that the patient would have survived this occlusion had not a second and a third severe insult to the heart occurred soon afterward. These also resulted from the thrombus described above. The sudden collapse three hours before death was probably synchronous with the passage of part of this thrombus, as an embolus, farther along the vessel. This sequence of events is supposed by many to be rather rare. Here also, if the blood clots interpreted as emboli had been found lying free in the vessel, rather than lightly adherent, there might have been some suspicion that the injection procedure had dislodged them from their original location.

CASE 19.—Fig. 16. Coronary thrombosis, cardiac infarct, rupture of the heart.

Clinical History.—The patient was a man, 50 years of age, who had been admitted to the hospital three years before with paroxysmal tachycardia and breathlessness. The electrocardiogram then showed left axis deviation, a diphasic T_2 and inverted T_4 . Under quinidine therapy, the heart rate quickly returned from 160 to normal. The patient said he had had several similar episodes during the previous

year. Three years later, for one week, he had daily substernal pain associated with marked dyspnea. These attacks were induced by mild exertion, exposure to cold, or excitement, and were relieved promptly by nitroglycerin. Finally, he had a more severe similar attack, lasting an hour, and accompanied by pain radiating down the left arm. On admission, the electrocardiogram showed normal rhythm, a rate of 90, left axis deviation, slight elevation of the S-T segment in Lead III, and a flat T_4 . Five days later, the electrocardiogram showed a rate of 110 and elevation of the S-T segment in Leads III and IV of the acute coronary type. The temperature was normal on admission, but next day rose to 102° F. and remained elevated until death. The blood pressure remained between 110/80 and 130/90. He had repeated attacks of substernal pain, usually relieved by nitroglycerin or morphine. On the fourth day, he suddenly became ashen and very short of breath, and expired. Autopsy showed that the heart had ruptured, producing hemopericardium.

Heart.—The heart weighed 430 gm. There were no valvular lesions. There was a large, fresh infarct in the posterior wall of the left ventricle. The extent of this infarct is indicated in Fig. 16 by the dotted line. At the anterior border of this infarct there was a tear of the myocardium 1 cm. long, indicated by a broken line. Elsewhere the myocardium was not unusual.

Coronary Arteries.—The coronary arteries showed only slight diffuse, but considerable localized, arteriosclerosis. Not a single plaque was found in the right coronary artery. A single small plaque (*A*) was found in the left descending coronary artery. The condition of the left circumflex coronary artery is of prime interest. In this vessel, a short distance from its origin, was an extensive area of arteriosclerosis with considerable narrowing, without calcification. This is shown in the roentgenogram at *B*. Deposited on this latter plaque was a large, occluding, dumbbell-shaped thrombus. No injection mass went past this thrombus, for the intima of the vessel in this region was entirely untinted over a length of about 7.0 mm. In the roentgenogram there is complete absence of shadow of injection mass in this zone. Nevertheless, the lumen of the open vessel just distal to this occluded zone shows a faint shadow of injection mass. On dissection, the intima here was found to be tinted pale blue, thus indicating that this injection mass had come entirely from the left coronary artery. Branches originating in this portion of the vessel distal to the occlusion were similarly injected. It is evident from the roentgenogram that this injection was by anastomotic channels from branches of the left descending artery. Again, although it was not possible to be sure about the dissection of such branches, several links which seem to connect can be found in the roentgenogram.

Careful study of the roentgenogram reveals the outline (*D*) of the left circumflex artery and its branches distal to this zone of anastomotic injection. In this region, however, the shadow of the lumen is less radiopaque than the surrounding heart tissue, rather than the reverse, as is the case when the lumen is filled with the mass. This is due to the fact that the vessel was distended with the salt solution which was used as a preliminary wash. The salt solution evidently ran into this vessel through the anastomotic channels more readily than did the injection mass. Probably if the injection pressure had been raised above the usual standard (150 mm. Hg), or if the injection time at this pressure had been prolonged, the injection of this vessel would have been more complete.

Comment.—In this heart the slow narrowing of a single coronary artery branch, followed by rapid occlusion of that branch and then sudden death four days later from rupture of the heart, presents a sequence of events such as one might plan experimentally. We have repeatedly found that in the normal heart the ligation of a single vessel just previous to injec-

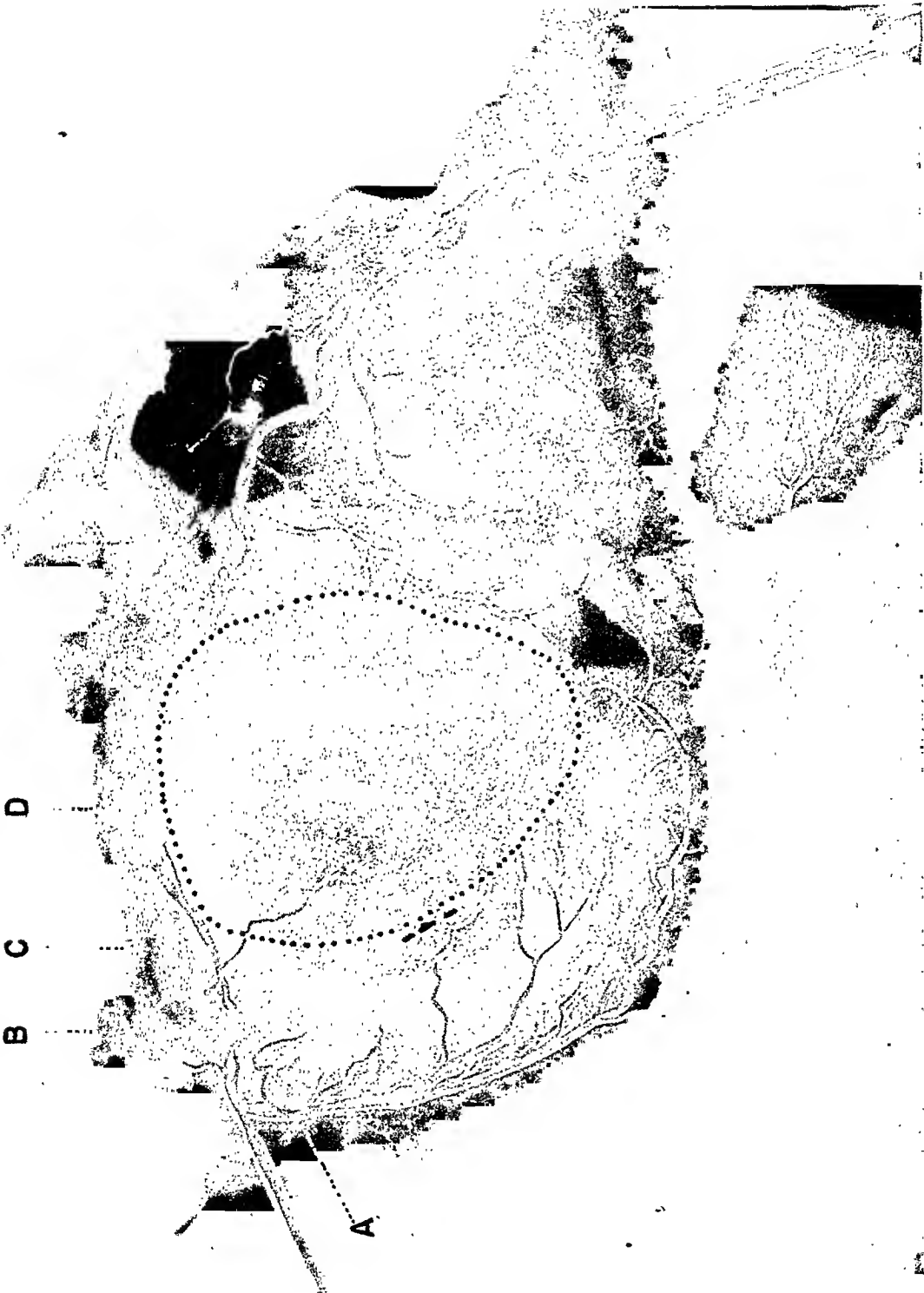


Fig. 16.—Case 19. (Illustration reduced to % normal size.)
A, Arteriosclerotic plaque
B, Occluding thrombus
C, Anastomatic injection
D, Uninjected vessel.

tion never results in anastomotic injection beyond the ligature. The anastomoses found in this heart bridging the completely occluded zone probably did not develop during the four days between the sudden acute occlusion and death. It seems more probable that they were being established during the progressive course of the gradual narrowing of the left circumflex artery. The slow narrowing could probably have gone on to complete occlusion without the formation of an infarct. The sudden thrombotic occlusion before the anastomotic circulation was ready resulted in infarction and death.

DISCUSSION

There are two essentially new procedures in the method here described for studying the cardiac circulation: First, a dissection of the heart was devised which unrolls the unfixed heart in such a way that the complete coronary artery tree is laid out in practically one plane, resembling a diagram. Second, a new radiopaque injection mass which permits such a dissection of the fresh, unfixed heart was used. The basis of this mass is a solution of agar-agar. To this an insoluble lead salt was added. Although it is ideal for this purpose, agar has been seldom so used. It can be kept indefinitely in liquid form at a comparatively low temperature (45° C.), can be immediately hardened by chilling, and will not liquefy again at room temperature. None of the various metals, waxes, starches, gums, celloidin, or gelatin previously used are as satisfactory as agar. Lead was arbitrarily selected for the radiopaque substance because of its high molecular weight and high relative radiopacity in comparatively low concentrations. However, since there are no limitations due to the dangers of toxicity as there are in the living patient, other metals, such as bismuth or mercury, might prove to be more satisfactory than the more commonly used barium. Complications such as the effect on the solubility and coagulability of the agar, uniformity and small size of the particles, effect on the tissue injected, etc., enter into such a selection. We have used the lead phosphate agar as prepared above throughout this series because it was the first to prove satisfactory, but we are continuing our experiments with various other methods of preparation and various other salts in combination with the agar base.

Direct comparison of this lead-agar with the more commonly used barium-gelatin has shown that we obtain as satisfactory roentgenographic shadows with 15 per cent lead phosphate as with 30 per cent barium sulfate. The gelatin, of course, remains solid at room temperature only after fixation in formalin. At the injection temperature of 45° C. the lead-agar is considerably more fluid than the barium-gelatin. Relative to human heparinized blood at 37° C., and tested on the same viscosimeter, the lead-agar has a viscosity of three and the barium-gelatin of eighteen. This extremely high viscosity of the barium-gelatin is due to

its high content of both gelatin and barium sulfate. It is desirable to keep the viscosity of the injection mass as low as is consistent with the other properties which such a mass must have. The great difference in the viscosity of these two masses is, however, not directly reflected in their ability to penetrate into the small arterioles. Both reach vessels of about the same caliber. For arterial visualization, an injection mass which would pass through the capillaries would be useless, but it should penetrate almost to them. The size of the largest particles present in the mass is probably an important factor in this uniform penetrability. Our ultimate aim is to prepare a mass which will have the desirable properties of the present lead-agar mass, but will give an even more detailed picture of the coronary artery tree.

In the procedure as described, it is easily possible, with the dissecting scissors, to open up and follow vessels of a diameter of 1.0 mm., or slightly less, especially when their intimas are brightly colored and the vessels are filled with a mushy agar plug. We regularly lay open all the coronary arteries as far as branches of that caliber in all injected hearts. If the vessels are not opened, they may be traced even further as thin, white, pencil lines, due to their content of semisolid injection mass. Only on rare occasions, however, have we been able to connect two open lumina by white streaks which could not be opened. By actual micrometer measurements on the roentgenograms, we know that vessels with lumina as small as 200 micra are regularly visualized. The finest twigs shown in the roentgenogram can never be dissected out, of course. Measurements with the micrometer ocular on the microscopic sections show that in normal hearts the lead-agar mass always penetrates to arterioles 40 micra in diameter, reaches about 50 per cent of the vessels 20 micra in diameter, and never injects vessels smaller than 10 micra in diameter. Table V sums up these various measurements and the conclusions to be drawn from them. The general statement can be made that, with the method used, anastomoses, when they occur, are present in small arterioles only.

TABLE V
ZONES OF CORONARY ANASTOMOSES

ZONE	DIAMETER OF VESSEL (MICRA)	METHOD OF PROVING CONTENTS OF VESSEL	ANASTOMOSES
1	> 800	Lumen opened with dissecting scissors	Anastomoses proved only once
2	800 to 501	Dissectible but without opening lumen	Anastomoses rarely proved
3	500 to 201	Visualized by x-ray but not dissectible	Anastomoses probable but unproved
4	200 to 40 to 10	Injected but not visualized by x-ray	Anastomoses usual and proved
5	< 40 to 10	Not injected by mass	Anastomoses ?

There is a large, unexplored territory between arterioles of these dimensions and the capillaries. In this territory lie the vessels to the

valves which we have never succeeded in injecting with the lead-agar. The connections with the Thebesian channels will also be found in this uninjected territory since there was never any leak of the injection mass into the chambers of the heart. Information on these problems awaits the preparation of a more nearly perfect mass. Injections of these structures in continuity with the coarser circulation will yield many new facts. The method of unrolling the heart and laying out all these structures in one plane should permit many new studies to be made. The data presented above apply only to the arteries of the ventricles. The anricular branches are less constant in their origin and course and practically never become occluded. The few branches going to the anricles are easily followed in the roentgenogram of the unrolled heart. Their paths will be the subject of a separate communication.

The dissection devised for the purpose of disentangling the arteries has unexpectedly proved to be superior in other respects to the traditional incisions for opening the heart. After this dissection all the endocardial structures are simultaneously available for inspection on one side of the specimen, and all the pericardial surface on the other side. It is much the same as opening a single-chambered hollow viscus, such as the stomach. When it is desired to open the heart only for a routine examination, the complete dissection is slightly modified. A single incision through the middle of the interventricular septum from the base of the heart to the apex is then substituted for the incisions devised to remove this septum.

Except for the reading of the roentgenograms and the final detailed dissection of the doubtful vessels, the method described is simple enough so that it can be entrusted entirely to a technician. The conditions of the injection are definitely standardized and constant, and require almost no adjustment in individual hearts. In our more recent series unsuccessful injections are rare, even in the hands of an assistant unskilled in the use of the method. A surprising amount of information about the condition of the circulation in an individual heart, much of which would otherwise have been overlooked entirely, can be obtained from even a partially successful injection by this method. We have never had an uninformative roentgenogram.

We have placed so much emphasis upon the method used because it is our belief that much of the confusion in the literature about the effect or lack of effect of occlusions of the coronary arteries and the ability of the collateral anastomotic circulation to compensate for such occlusions is due to unsatisfactory methods of study. No absolute statements on the above questions could be made for any individual heart unless every artery down to the smallest arteriole had been examined. The nearer the method approaches that ideal, the better the results. For each individual vessel, one must know whether it is patent throughout its whole

length, and, if patent, what is the source of its blood supply. Only if all these data were available, could one fully interpret the possible effects of such occlusions as may be found.

The combination of a multicolored radiopaque injection material and a complete dissection gives more information than any other method yet devised. Injections without dissections, no matter whether visualized by corrosion, clearing, or x-ray, miss occlusions and appear to show anastomoses between large vessels which actually do not exist. Dissections without injections miss occlusions also and are notoriously incomplete in other respects. Repeated reference to the roentgenogram of the injected vessels in the unrolled heart during the course of the dissection serves as a constant stimulus to attempts to dissect out anastomotic channels apparently present in the roentgenogram. Also, the distribution of the multicolored injection mass in the arteries as they are opened directs attention to possible and unsuspected channels of flow shown in the roentgenogram. At the end of such a dissection one is justified in concluding that every possible occluded spot in the coronary artery tree has been found and that an attempt has been made to dissect out every possible anastomotic channel. Conversely, when no occlusions or anastomoses can be found, one is equally sure that none existed. Our confidence in these conclusions has been built up only after many exasperatingly unsuccessful attempts to dissect out an anastomotic connection which we knew must be present. When the whole right coronary system has been injected with the blue mass from the left coronary artery, as in Fig. 13, or when the vessels throughout show a variegated picture of red, blue, and various shades of purple in the vessels supplied by both canulae (Fig. 15), there must be a very rich anastomotic circulation present even if it cannot be followed with the dissecting scissors or in the roentgenogram.

Thus, for final proof of anastomosis, we rely very little on the roentgenogram or on our ability to dissect out the actual connecting channel. These procedures give evidence of the amount and distribution of arteriosclerosis and points of narrowing and of occlusion. The evidence for anastomotic circulation is drawn largely from the distribution of the multicolored mass in the dissected vessels. In this group of 35 hearts taken from patients over 50 years of age, these procedures taken altogether have shown a rich anastomotic circulation in only those hearts in which there was occlusion of the coronary arteries. Such zones of anastomotic circulation were not distributed indiscriminately, but in each individual heart the anastomoses were specifically designed to compensate for the occlusion. The compensatory blood supply usually came from the left coronary artery, no matter where the occlusion was, but the reverse was occasionally true. However, with this method which so readily showed the intimate details of an anastomotic circulation when

it was present, we could not demonstrate any anastomoses in normal hearts in which there were no occluded coronary arteries. Others who have reported coronary artery anastomoses in normal senile hearts usually give few data as to their criteria for the selection of "normal" hearts. Throughout their reports, increase in the amount of arteriosclerosis with increase in age is tacitly acknowledged. The amount of arteriosclerosis which they accept as "normal" for each age group is not clear. Our series is at present too small to permit grading of the amount of arteriosclerosis in each age group. Inasmuch as there is a direct relation between the degree of anastomosis and the degree of arteriosclerosis in the series as a whole, we feel that a similar relation will be found within each age group. It thus seems that anastomoses in the coronary artery system do not develop *pari passu* with increase in age, but only when and where there is need for them. Then and there they develop quite easily and readily and usually to a sufficient degree to compensate adequately.

From an anatomical viewpoint this may appear to be a satisfactory circulation. It seems, however, that there must often be a greatly disturbed physiologic balance. Thus when, as in Fig. 13, the blood flow through the whole of the right coronary artery moved from its narrower peripheral end to its wider, more central end, there must have been some functional disarrangement of the flow. The arteries do not serve as mere inert tubes for the passage of blood, but their complicated muscular and elastic tissue walls are also concerned in the local control of that flow. When the flow through a vessel is in the opposite direction to that for which the artery was designed, there must be some disturbance of function. Such disturbances must occur on occasion in different locations in hearts in which certain parts are being nourished by an anastomotic circulation. Perhaps this flow in the wrong direction, so to speak, has some relation to anginal pains.

The emphasis throughout this report has been upon coronary artery occlusions and anastomoses. We have studied five hearts without occlusions, but with anastomoses. They were from patients whose ages varied from 5 to 77 years. None showed more than a few scattered plaques of coronary arteriosclerosis. All these hearts, however, were markedly abnormal in other respects. Other equally abnormal hearts (but without arteriosclerosis or occlusions) showed no anastomoses. Thus, although coronary artery occlusion is the commonest cause of the development of coronary artery anastomosis, it is not the only one. Only a complete study of a larger series of hearts which are the seat of pure valvular disease or have been damaged by hypertension will explain why some develop anastomoses and other do not. Probably here also these anastomoses develop only when and where they are needed.

When an artery is completely occluded, the need for a new channel to carry the blood around the obstruction is obvious. Arteriosclerosis, the outstanding cause of occlusions, is a slowly, steadily progressing lesion, with much narrowing before the final complete block. This narrowing, in itself, surely creates a need for anastomoses, and, as illustrated in Case 19, the anastomoses form. With the proper technique, it is comparatively easy to find all complete occlusions. It is much more difficult to make even a rough estimate as to how much partial obstruction is present at any one spot. Although Saphir and his associates concluded that at least two vessels must be affected to give rise to an infarct, in their series of 30 infarcted hearts only 11 (37 per cent) showed complete occlusion in branches of two of the three major divisions of the coronary arteries. Four (66 per cent) of the six more carefully studied infarcted hearts we examined showed such double occlusions. Many of the hearts we studied showed marked arteriosclerosis in two or more major branches without infarcts. The important point to emphasize is not the multiplicity of the lesions in the coronary arteries, but the speed with which the occlusion or narrowing develops. A rapid occlusion in one major branch, with all other branches normal, will result in an infarct, as in our Case 19. Slower narrowings, even if numerous, stimulate the development of anastomoses, and the heart is thus prepared for occlusion when it comes.

The roentgenograms of the unrolled injected vessels help greatly in the study of the relative vascularity of the right and left ventricle at various ages and under varying pathologic conditions. The length, caliber, and method of branching of every vessel can be plainly seen. We are at present measuring these factors in order to correlate them with the weight, thickness, and nature of the disease of the myocardium of the two ventricles. The obvious excess of the number of branches of the left coronary artery over the right is the only clue we have at the present time as to why occluded branches in either artery usually obtain at least some of their compensatory channels from a branch of the left coronary artery.

Even in normal hearts there is a consistent absence of large vessels over a small area in the posterior wall of the right ventricle near its base. This apparently avascular area is very thin and never fibrosed. Infarcts in this area are very rare (Saphir did not find one), and it seems probable that normally it is largely nourished by the Thebesian vessels. Investigators of these vessels might well concentrate on this area.

CONCLUSIONS

1. The coronary arteries, in *normal* human hearts, even senile hearts, are true Cohnheim end arteries, without anastomotic connections; such anastomoses do not develop *pari passu* with increase in age.

2. Anastomoses always develop readily *whenever* and *wherever* arteriosclerotic narrowing or occlusion causes obstruction in the coronary artery circulation; these anastomoses are localized to the regions where they are needed.

3. To ascertain accurately the site and effects of all coronary artery occlusions and anastomoses in individual hearts, it was necessary to devise a method capable of *completely* and *simultaneously* visualizing the *entire course* of all arterial branches so that they could be studied in detail. This has been accomplished by a simple standardized method utilizing (a) a newly devised multicolored radiopaque injection mass, (b) a new method of cutting open the injected heart, and (c) a complete dissection of the colored coronary artery tree.

4. The new injection mass consists of a suspension of lead phosphate in agar, colored differently for the right and left coronaries. It is injected at 150 mm. Hg pressure, at 45° C.; it sets quickly and permits immediate cutting and radiography of the fresh unfixed heart.

5. The new method of opening the heart unrolls all the coronary arteries so that they lie in one plane and avoids overlapping of the roentgenographic shadows of the injection mass within them.

6. The distribution of the multicolored mass in the dissected coronary artery branches gives an absolute index of the distribution of the blood from either coronary artery orifice.

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THE ROLE OF NUTRITIONAL DEFICIENCIES IN THE PRODUCTION OF CARDIOVASCULAR DISTURBANCES IN THE ALCOHOL ADDICT*

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IT IS well-known that alcohol addicts who have no history of cardiovascular or kidney disease, and no demonstrable arteriosclerosis or persistent hypertension, frequently show signs and symptoms referable to disturbances of the circulatory system when they have recovered from the immediate effects of their inebriety. This study was undertaken in an effort to clarify the nature and relative frequency of these manifestations, and to evaluate the relative importance of alcohol and dietary deficiency as etiologic factors. The latter is of especial significance because other complications of alcohol addiction, such as polyneuritis,¹⁻⁵ pellagra,^{6, 7} and alcoholic stomatitis⁸ have been shown to be due to dietary deficiency rather than to the direct action of alcohol.

SELECTION OF CASES

The 83 subjects of this study were the alcohol addicts between the ages of 27 and 51 years, inclusive, who were admitted to this service during the year ending June 1, 1937, for treatment of the conditions indicated in Table I, who did not have and never had had, as far as we could ascertain, chronic cardiovascular or acute or chronic kidney disease, and had improved or recovered when they were discharged from the hospital.

Eighteen of these 83 patients showed none of the stigmas (Table I) of alcohol addiction. The diagnosis of alcohol addiction was made in

TABLE I
DISTRIBUTION OF COMPLICATIONS IN THE ALCOHOL ADDICTS STUDIED

	WITH PERIPHERAL NEURITIS	WITHOUT PERIPHERAL NEURITIS	TOTAL
Peripheral neuritis only	25	—	25
Alcoholic encephalopathy or Korsakoff's syndrome	16	2	18
Pellagra*	12	0	12
Laënnec's cirrhosis	7	2	9
Scurvy	1	0	1
	—	—	—
Total complicated	61	4	65
Uncomplicated			18
			—
Total subjects			83

*Includes two cases of alcoholic stomatitis.

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this group of "uncomplicated" subjects on a record of at least two admissions to the alcoholic ward of this hospital within one year previous to the time when they were selected for study.

METHODS

Upon admission to the medical service each patient was given the basal diet⁴ which is of borderline adequacy in its content of vitamin B₁ for persons weighing from 58 to 63 kg.; the intake of fluid and salt was not restricted. Only those who, because of the severity of their peripheral neuritis or encephalopathic manifestations, were unable to be up and about the wards were kept in bed. During this preliminary period, which lasted from four to fourteen days, no specific medication was given, and the cardiovascular status of each subject was studied. This study included (1) a history of the present illness, covering the diet and any previous acute or chronic diseases, as elicited from the patient and verified, whenever possible, through friends and relatives; (2) detailed physical examination at daily intervals, including daily weighing; (3) complete blood count; (4) plasma protein determinations within twenty-four hours following admission to the medical service; (5) repeated blood pressure determinations; (6) a teleoroentgenogram of the heart; (7) an electrocardiogram using the three standard leads, made as soon as the subject was able to cooperate; and (8) complete urinalysis, which was repeated if indicated.

At the completion of the above studies, and after the patient had reached a constant weight level, the 65 patients with complications who showed in addition to their alcohol addiction one or more of the diseases listed in Table I were maintained with a weighed diet rich in vitamins, supplemented by 18 gm. of vegex daily. In addition to 3,100 calories, this regimen supplied 1,065 international units of vitamin B₁ daily, which was approximately four times their estimated maintenance requirement of vitamin B₁.⁹ This therapy was maintained for periods varying from two weeks to two months. In ten instances the oral therapy was supplemented by daily intravenous injections of 10 mg. of crystalline vitamin B₁,¹⁰ and three patients received 50 mg. of crystalline vitamin B₁ daily by parenteral administration. The studies outlined above were repeated at intervals throughout the period of observation and again before discharge.

The 18 alcohol addicts who showed none of the stigmas of alcohol addiction did not receive specific treatment, and the initial studies were not, as a rule, repeated.

RESULTS

The data accumulated were analyzed by two methods. First, a comparison was made in the group with complications before and after the period of vitamin therapy. Second, observations made during the control period on the group with complications were compared with those made on the group without complications.

The results by the first method of study are summarized in Table II and are described below. Eight (12.3 per cent) of the entire group of 65 patients complained of cardiac palpitation on admission to the medical wards. Twelve (18.4 per cent) were troubled by shortness of breath on slight exertion. Two complained of pain over the heart in addition to shortness of breath, and one complained only of precordial pain. Three patients presented marked cyanosis of the nail beds on admission to this service. These signs and symptoms were present singly or in combination in a total of 19 of the subjects (29 per cent). In

every instance these evidences of cardiovascular dysfunction disappeared within four days following admission to the medical wards, and before any therapy other than sedation was instituted.

Mild to severe edema was present in 20 patients, two of whom had anasarca. In addition to the edema, 18 of these patients (90 per cent) showed other signs of circulatory distress. On admission, 13 had one or more of the following symptoms: palpitation, dyspnea, precordial pain, cyanosis. In 12 instances the liver was enlarged and palpable, and 4 of the patients had cardiac murmurs.

TABLE II

INCIDENCE AND TYPE OF CARDIOVASCULAR DISTURBANCES IN THE GROUP WITH COMPLICATIONS AND INCIDENCE OF CHANGES FOLLOWING THERAPY

	NO. OF CASES ON INITIAL STUDY	NO. OF CASES IN COL. 1 IN WHICH STUDIES WERE REPEATED AFTER THERAPY	NUMBER IMPROVED AFTER THERAPY	PER CENT IMPROVED
Symptoms due to cardiovascular dysfunction	19	19	19	100.0
Edema	20	20	20	100.0
Palpable liver	26	26	14	53.9
Cardiac murmurs	9	9	8	88.9
Enlarged heart (x-ray)	14	8	4	50.0
Systolic blood pressure above 150	15	15	14	93.3
Diastolic blood pressure above 100	9	9	8	88.9
Abnormally large value for $K : Q \cdot T = K \sqrt{R - \bar{R}}$	20	10	5	50.0
Low voltage of QRS in all 3 leads	1	1	1	100.0
Low voltage of T-waves in all 3 leads	6	4	3	75.0
Inverted T-waves in 1 or more leads	25	15	11	73.3
Depressed S-T segments	10	10	10	100.0
Right axis deviation	3	3	3	100.0
Left axis deviation	16	7	4	57.1

In 12 cases the edema disappeared after the first day in the hospital and did not recur, although these patients were kept out of bed as much as possible during the day. Three patients on our basal diet,⁴ with an unrestricted fluid intake, and without absolute bed rest lost their edema gradually over a period of three or four days. In 4 cases the edema did not disappear until after the institution of high vitamin therapy. In one patient who showed anasarca on admission, mild pitting edema of the lower extremities was still present when he was discharged fifty-one days later.

Sixteen patients who presented the above signs and symptoms of cardiovascular dysfunction had enlarged, palpable livers on admission. In 12 instances the enlarged liver was associated with edema, and in 7 of these the liver had decreased greatly in size or was no longer palpable at the time of discharge from the hospital. A definite diagnosis of hepatic cirrhosis was made in 3 instances in which the liver remained unaltered in size. The liver decreased considerably in size in one patient in whom a diagnosis of cirrhosis had been made.

Enlarged livers were palpated on admission in 10 patients who presented no other clinical evidences of cardiovascular disturbance. In 7 instances the liver was no longer palpable at the completion of the study period. One patient with cirrhosis revealed no alteration in the size of the liver, and another with a diagnosis of cirrhosis showed, after institution of the high vitamin regimen, a decrease in the size of the liver to a point where it was no longer palpable when he was discharged.

The average heart rate at the completion of the period of hospital care was 92, as compared with an average of 101 on admission.

Of the 9 patients with cardiac murmurs on admission, 3 had systolic murmurs heard only at the apex. In 2 cases a systolic murmur was audible only over the aortic area; a systolic murmur audible at both base and apex was heard in 3 instances; systolic and diastolic murmurs at the base alone were present in one case. Persistence of a murmur throughout the period of hospitalization occurred in only one instance; this patient had a short rough systolic murmur over the aortic area which was not transmitted.

Of the 14 patients with roentgenographic evidence of cardiac enlargement, 7 had left axis deviation; one had right axis deviation; and 6 had no abnormal deviation of the electrical axis. Teleoroentgenograms were repeated before discharge in 8 instances, in 4 of which the size and the shape of the heart shadow were within normal limits. Of these 4 patients, one had shown right axis deviation, and 3 left axis deviation; all returned to normal before the final teleoroentgenogram. In only one of the four subjects whose cardiac enlargement persisted was there an associated deviation of the electrical axis (left) throughout the period of observation.

A comparison of the average admission blood pressure of the group without complications with that of the group with complications does not reveal significant differences. These figures, however, require further analysis. If the patients admitted in circulatory collapse are omitted from the group with complications, we obtain a value of 141/90, as compared with 134/84 for the group without complications. We find also that in the complicated cases there was a range in blood pressure values from 106/70 to 190/120, with systolic blood pressures above 150 in 15 cases (23 per cent) and with diastolic blood pressures of more than 100 in 9 (13.8 per cent). The range in blood pressure values in

the group without complications was 110/70 to 160/100 with only 2 patients (13 per cent) presenting a systolic pressure over 150, and none a diastolic pressure above 100.

Analysis of the final blood pressure readings in the complicated cases reveals a range of 95/60 to 162/105, with an average of 121/81. At the time of discharge only one patient (1.5 per cent) presented a systolic pressure above 150, and only one (1.5 per cent) a diastolic pressure above 100.

In 20 subjects (30.7 per cent) the relation of ventricular systole (Q-T interval) to the entire cardiac cycle (R-R interval), as measured in the initial electrocardiograms and expressed by the constant K of Cheer and Dieuaide,¹¹ was above the normal values (0.433 for males and 0.456 for females) of Shipley and Halloran, as given by Feil.¹² Tracings were repeated before discharge in 10 instances. In 5 the value of K returned to normal limits. In no case was there an increase in K above that calculated from the initial electrocardiogram. In 4 of the 45 patients (69.3 per cent) whose initial values for K were within normal limits a later rise above normal occurred. We were unable to correlate the changing values for K with variations in the heart rates of these patients. Seventeen (85 per cent) of the group of 20 patients with high initial values for K showed clinical evidence of cardiovascular dysfunction on admission, but 14 (31.1 per cent) of those with initial values for K within the normal range also showed clinical evidence of cardiovascular dysfunction.

The one patient with low voltage QRS complexes in all three leads during the control period developed an increase to normal voltage before discharge.

Additional electrocardiograms were made before discharge in 15 of the 25 cases in which the T-wave had been inverted in one or more leads when the first tracing was taken; in 11 of these the T-wave had regained the upright position. This group included the 3 patients with inversion of the T-waves in all three leads and the 2 who showed an initial inversion of the T-waves in Leads II and III. Of the 4 patients who showed no change, 3 had had inverted T-waves in Lead III alone, and the fourth an inverted T-wave in Lead I with a diphasic T-wave in Lead II. None of these patients received digitalis.

Four of the 6 patients who had shown initial low voltage T-waves in all three leads had electrocardiograms again before discharge, and in 3 there was a return to normal voltage.

The depression of the S-T segment which had been present initially in 10 patients disappeared in each case after treatment.

All 3 patients who had right axis deviation on admission lost it before they were discharged. Electrocardiograms were repeated before discharge in 7 of the 16 cases of left axis deviation, and in 3 of these there was no abnormal deviation of the electrical axis.

In no case in which there was edema on admission was the serum albumin below 2.5 gm. per cent, or the total serum protein below 5 gm. per cent. The average total serum protein was 6.24 gm. and the average albumin-globulin ratio 3.77: 2.47. These figures are slightly lower than the average for the entire group of subjects with complications.

Some degree of anemia was present in 13 of the 20 patients who had edema on admission, which is an incidence of 65 per cent, whereas the incidence of anemia in the "complicated" group as a whole was 72.4 per cent.

TABLE III

A COMPARISON OF THE CARDIOVASCULAR STATUS OF THE "UNCOMPLICATED" GROUP WITH THE "COMPLICATED" GROUP DURING THE CONTROL PERIOD

	UNCOMPLICATED	COMPLICATED
No of cases: Male	13 } 18	47 } 65
Female	5 }	18 }
Extremes in age	28—49	27—51
Average age	38	40
Previous heart disease	0	0
Cardiovascular symptoms	0	19 (29%)
Edema	0	20 (30.7%)
Palpable liver	0	26 (40%)
Average heart rate	88	101
Cardiac murmurs	0	9 (13.8%)
Enlarged heart (x-ray)	0 (out of 15)	14 (out of 55 = 25.4%)
Average blood pressure	124/84	136/87
Extremes of K: Male	0.3745—0.4318	0.3500—0.6306
Female	0.3946—0.4341	0.4041—0.5181
Average K: Male	0.4021	0.4323
Female	0.4107	0.4390
Low voltage of QRS in all 3 leads	1 (5.5%)	1 (1.5%)
Low voltage of T-waves in all 3 leads	1 (5.5%)	6 (9.2%)
Inverted T-waves in Lead I	0	1
in Lead III	3	19
in Leads II and III	0	2
in all 3 leads	0	3
Depressed S-T segments in Leads I and II	0	1
in Lead II	1	1
in Leads II and III	0	8
Right axis deviation	0	3 (4.6%)
Left axis deviation	1 (5.5%)	16 (24.6%)
Average plasma protein	6.52	6.32
Albumin	4.18	3.82
Globulin	2.34	2.5
Anemia		
Mild	2	12
Moderate	0	21
Severe	0	9

We were unable to correlate the variations in blood pressure readings of the patients with complications with the presence or absence of

anemia. Those without anemia had an average blood pressure of 144/94; those with a mild or moderate degree of anemia averaged 145/91; and those with a severe degree of anemia averaged 142/93. The range in blood pressure was practically the same in all groups.

The results by the second method of study are summarized in Table III. The preponderance of signs and symptoms of cardiovascular dysfunction in the complicated cases, as compared with the uncomplicated cases, is obvious. Nineteen patients in the "complicated" group had dyspnea, palpitation, precordial pain, or peripheral cyanosis on admission; 20 had pitting edema; and 25 had enlarged, palpable livers, whereas no patient in the "uncomplicated" group presented any of these signs. A comparison of the electrocardiograms shows a much greater incidence of inverted T-waves and depressed S-T segments in the complicated cases than in the uncomplicated cases.

In 20 subjects in the group with complications the relation of ventricular systole to the entire cardiac cycle was prolonged beyond the normal limits. No patient in the group without complications showed an abnormally large K. The patients in the "complicated" group revealed a higher incidence of tachycardia, and a greater incidence and severity of anemia, but there was no significant difference in the plasma protein levels of the two groups.

COMMENT

All the subjects of this study were alcohol addicts, but clinical evidences of cardiovascular dysfunction were found only among those patients who had one or more of the complications listed in Table I. It would appear, then, that alcohol per se is probably not the cause of the cardiovascular disturbances which occur in the alcohol addict. Of the 65 patients in the group with complications, 61 had polyneuritis on admission. There is abundant evidence to indicate that the primary etiologic factor in the polyneuritis of the alcohol addict is vitamin B₁ deficiency.¹⁻⁵ Of the four patients who showed no definite clinical signs of polyneuritis, two appeared to have the Korsakoff syndrome. The relatives of one of these patients said that he had eaten only one meal daily during the past year, and the other, who had had a posterior gastroenterostomy performed nine months before, had eaten irregularly for the preceding four months. Of the remaining two patients, one complained of a poor appetite of several months' duration, with persistent vomiting during the week immediately preceding; and the other admitted imbibing one quart of whisky daily for the past year, with irregular meals consisting of soup and sandwiches during the three weeks prior to admission. It is obvious that definite and severe dietary deficiencies were present in all of these 65 complicated cases.

The onset of symptoms referable to cardiovascular dysfunction was acute or subacute in every case, occurring from two days to two weeks

before admission, and the symptoms were progressive. When palpitation, dyspnea, and precordial pain occurred, they were usually the first signs to be noted by the patient. In addition to one or more of the above, a typical patient presented the following: Dependent edema, tachycardia, elevated systolic blood pressure, a palpable liver, a moderate degree of anemia, slight cardiac enlargement, a systolic murmur, and electrocardiographic abnormalities such as depression of the S-T segments, inverted T-waves, and prolongation of the constant K of Cheer and Dieuaide.¹¹

In several instances it was observed that the degree of edema appeared out of proportion to the amount of demonstrable cardiac disease. In two subjects with extensive edema there were no signs or symptoms of cardiac embarrassment. The venous pressure was measured in one of these cases and found to be within normal limits.

The patients with signs and symptoms of cardiovascular dysfunction tended to improve when nothing was done except to keep them in bed on the basal⁴ diet, but improvement was hastened in every case when the vitamin-rich diet was substituted for the vitamin-poor diet, and in four cases no improvement whatever was observed until after a high vitamin regimen had been instituted.

As these patients had been on diets deficient in a multiplicity of necessary food elements and were treated with diets rich in protein, fats, carbohydrates, and all the vitamins, it is difficult to say that any one of these factors was responsible for the disease or its cure.

It is well known that prolonged and severe deficiency of protein in the diet may cause considerable edema and many signs of cardiovascular dysfunction. However, in this series of cases, although the average serum protein level in the group presenting edema was somewhat lower than the average of the entire group, no patient had a total serum protein level below 5 gm. per cent, or a serum albumin below 2.5 gm. per cent. The range in values for total serum proteins and albumin fractions was as great in those who had edema as in those who did not.

Of the patients in the group with complications, 72.4 per cent presented some degree of anemia. A careful analysis of the figures, however, fails to reveal any correlation between the severity of the anemia and the number or severity of signs of cardiovascular dysfunction, including edema. As a matter of fact, several patients with severe edema and other signs of cardiovascular disturbance had no anemia.

The part played by a deficiency in the fat-soluble vitamins A and D in the production of these disturbances is probably negligible. First, these patients presented none of the well-recognized clinical evidences of deficiency in either vitamin A or D. Second, these vitamins are well stored in the body, and patients whose diets are deficient in all respects may therefore be expected to present signs of deficiency in one or more of the water-soluble vitamins long before evidences of vitamin A or D

deficiency are discernible. Platt and Lu¹³ point out that "in high degrees of vitamin B₁ deficiency, signs of vitamin A deficiency are not seen except occasionally in minor forms, and when there are marked evidences of vitamin A deficiency, the manifestations of vitamin B₁ lack are submaximal." As indicated above, 61 of our patients showed definite evidences of vitamin B₁ deficiency. In studying the effects of the various vitamin deficiencies upon the electrocardiogram of the rat, Drury, Harris, and Maudsley¹⁴ found that "of the vitamin deficiencies tested, A and D, separately and combined, appear to exert no characteristic influence upon the rhythm of or the conduction in the heart or upon the T-waves."

Only one of the 65 patients in the group with complications showed clinical evidence of scurvy. This individual had, in addition, a severe degree of peripheral neuritis.

The part played by vitamin B₂ (vitamin B₂ signifying the entire vitamin B complex minus B₁) in the production of both peripheral neuritis and cardiovascular disturbances in the alcohol addict is questionable. In an electrocardiographic study of 38 cases of pellagra, Feil¹² reports changes similar to those found in beriberi and in this study. Thirty-seven of his patients were alcohol addicts, and one was the victim of partial starvation. He reports that all of his patients had "the typical picture of pellagra with cutaneous, gastrointestinal and neurological symptoms of varying degree."

It is important here to point out that the neurologic symptoms occurring in alcohol addicts with pellagra are frequently seen in alcohol addicts who present none of the cutaneous, gastrointestinal, or mucous membrane lesions of pellagra. By far the most common of these neurologic manifestations in both groups is peripheral neuritis. The relationship of vitamin B₁ deficiency to the neuritis of the alcohol addict has been adequately demonstrated.¹⁻⁵ As the diet in Feil's cases was deficient in both vitamin B₁ and vitamin B₂, as all of his patients presented neurologic symptoms which from our studies^{3, 4, 5} appear to bear a closer relationship to vitamin B₁ deficiency than to pellagra,* and finally, as his findings were similar to those reported in endemic beriberi, it is probable that the cardiac symptoms reported by him were in fact manifestations of vitamin B₁ deficiency. Porter and Higginbotham,¹⁵ in a study of 25 selected cases of endemic pellagra, concluded that: "(1) The clinical evidence and necropsy studies show that the hearts of endemic pellagrins are normal or subnormal in size. (2) There are no characteristic electrocardiographic changes in endemic pellagra. Those changes that do occur are invariably explained by vascular or toxic complications. (3) Beriberi and pellagra have no comparable

*Since the submission of this paper for publication T. D. Spies and C. D. Aring (The Effect of Vitamin B₁ on the Peripheral Neuritis of Pellagra, J. A. M. A. 110: 1081, 1938) have confirmed this observation that the peripheral neuritis in pellagrins is primarily a manifestation of vitamin B₁ deficiency.

effect on the heart. The difference is so absolute that one ventures the opinion that B₁ is not concerned with the pathogenesis of pellagra."

That cardiovascular disturbances occur in beriberi is well known. This disease is frequently classified as follows: (1) the neuritic type, (2) the edematous type, (3) the mixed type, and (4) the cardiac type.¹⁶ The similarity between the manifestations of cardiovascular dysfunction described in endemic beriberi^{12, 16-20} and those presented in this study is striking. Indeed, our cases can be fitted accurately into the above classification of endemic beriberi.

Weiss and Wilkins²¹ studied the nature of the cardiovascular disturbances in vitamin deficiency states in 97 patients admitted to Boston City Hospital, a large proportion of whom were alcohol addicts. In general, their findings agree with those of this study. They noted that in "patients with cardiac dilatation, peripheral arterial sounds, rapid peripheral flow and engorged veins occurred, but other patients with an identical type of deficiency showed pulmonary engorgement and the picture of left-sided failure." In some cases there was fatal collapse of the peripheral circulation simulating shock. We have already noted the protean nature of the cardiovascular disturbances which occur in alcohol addicts, and their similarity to those of endemic beriberi.

It is of interest here to point out that although right-sided enlargement of the heart is generally stressed in textbook discussions of beriberi heart disease, left-sided preponderance and diffuse enlargement frequently occur. There may be no notable change in the size or shape of the heart. Keefer¹⁶ points out that pure right-sided dilatation is not an essential manifestation of beriberi heart disease. Scott and Herrmann,¹⁷ in a study of eight cases of beriberi in Louisiana, reported a moderate enlargement of the heart in only two cases and a slight to moderate left ventricular predominance in electrocardiographic studies in every case. In this study we did not observe pure right-sided dilatation by roentgenographic examination, though in two instances there was a marked diffuse dilatation of the heart with right-sided predominance. Right deviation of the electrical axis on the initial electrocardiogram was observed in only three subjects, whereas left deviation occurred in 16.

In England Campbell and Allison²² have reported a series of eight cases of polyneuritis, in which the symptoms of cardiovascular dysfunction were more prominent than the neuritic signs. They made the following interesting observation: "The type of polyneuritis in which cardiac changes occur most prominently is beriberi. The cases described here bear some resemblance to the milder types of the disease as it is described in the East. Had these cases been seen in the Orient, it is not improbable that they would have been attributed to that cause. On the other hand, it is open to question whether the varied diet of the European could ever become so deficient in vitamin B as to give rise

to polyneuritis with cardiac changes." The last statement in this quotation is open to considerable question.

That beriberi is a manifestation of avitaminosis (B_1) is so well-recognized that further discussion is unnecessary. As pointed out by Weiss and Wilkins,²¹ "so far as is known at present, deficiency of vitamin B_1 is the only vitamin deficiency which is followed by disturbed function of the heart." Carter and Drury,²³ working experimentally with pigeons, and Drury, Harris, and Maudsley,¹⁴ working with rats, demonstrated changes in cardiac rate when these animals were kept on diets deficient in vitamin B_1 .

Edema is not as a rule observed in experimental animals whose diet is deficient in vitamin B_1 , although Peters²⁴ has shown that when salt solution is given to these animals their weight may increase as much as 50 per cent. This edema may be completely dispelled by giving small amounts of vitamin B_1 .

Peters²⁵ has demonstrated that there is an accumulation of lactic acid in the nervous tissue of pigeons fed with diets deficient in vitamin B_1 . He was unable to demonstrate any toxic substance, or to produce symptoms in normal birds by the injection of lactate. An accumulation of abnormal quantities of lactic acid in the blood stream has also been demonstrated in patients with endemic beriberi by Inawashiro and Hayasaka.²⁶ This has been advanced to explain the facts that beriberi patients easily accumulate a large oxygen debt and require an abnormally long time to repay it and that severe cardiovascular dysfunction occurs in those who, because their peripheral neuritis is comparatively slight, are most capable of muscular exertion, and to account for the peculiar edema of muscle and other tissue which is not of cardiac origin.

Inawashiro and Hayasaka²⁶ point out that "if in patients with beriberi the acidotic condition of the muscle caused by contraction becomes very marked, the blood vessels in the muscle will become contracted, which makes the blood flow slow and in turn magnifies the acidosis in the muscle, the lactic acid resynthesis being further disturbed. Thus in the patients of beriberi an important cause has been brought forward of a swelling as well as claw pain of muscle." This may be applied to cardiac as well as to skeletal muscle, and may account for the anginal pain noted in three of the subjects of this study.

The incomplete oxidation of carbohydrate associated with the accumulation of abnormally large quantities of lactic acid in the blood and other tissues of subjects with vitamin B_1 deficiency may be the cause of the high systolic blood pressure frequently observed in subjects with beriberi at the acme of the disease. The occurrence of an elevated systolic blood pressure was observed by Weiss and Wilkins²⁷ in their study of vitamin deficiency states, and by us in this study. Lambert and Gellhorn²⁸ have demonstrated that the rise of blood pressure caused by

oxygen deficiency is greatly augmented by small amounts of carbon dioxide which in themselves have no effect upon blood pressure.

Of the 65 patients with complications included in this study, 26 presented large livers on admission. In 10 instances this enlargement was not associated with other clinical signs or symptoms of cardiovascular dysfunction. Vitamin therapy was followed by a decrease in the size of the liver in 14 patients, 7 of whom were in this latter group. We are not prepared to state whether this hepatic enlargement was due to circulatory failure or to the fatty changes frequently noted at autopsy in the livers of alcohol addicts.

SUMMARY AND CONCLUSIONS

Of 83 alcohol addicts who presented no evidence, past or present, of chronic cardiovascular or acute or chronic kidney disease, 18 showed none of the stigmas of alcohol addiction or deficiency disease. The evidence of cardiovascular disturbances in this group without complications was minimal. Of the remaining 65 patients, 61 had peripheral neuritis, 2 had alcoholic encephalopathy without neuritis, and 2 had portal cirrhosis without neuritis. Twelve patients had both neuritis and pellagra.

In this group of 65 patients with symptoms of dietary deficiency there was electrocardiographic evidence of cardiovascular disturbance in 47 per cent, and clinical evidence in 32.3 per cent. Ten additional patients presented large palpable livers without other demonstrable evidence of circulatory failure. The problem of the relative rôles played by fatty infiltration and chronic passive congestion of the liver in the hepatomegaly of these 10 subjects was presented.

We have pointed out the close resemblance of the clinical picture presented by alcohol addicts with cardiovascular disturbances to the various types of endemic beriberi, and have discussed the part played by deficiency of various accessory food elements in the production of these disturbances.

In conclusion we feel that this study supports the belief that beriberi in all of its manifestations is found in alcohol addicts in this country. From the data here presented we cannot estimate the incidence of cardiovascular disturbances in alcohol addicts in general. Our studies indicate, however, that approximately one-third of the alcohol addicts who show vitamin B₁ deficiency in the form of peripheral neuritis present clinical evidence of some degree of cardiovascular dysfunction secondary to this deficiency.

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A STUDY OF MYOCARDIAL HYPERTROPHY OF UNCERTAIN ETIOLOGY, ASSOCIATED WITH CONGESTIVE HEART FAILURE

WITH CONSIDERATION OF THE RÔLE OF ANTECEDENT HYPERTENSION*

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THAT congestive heart failure, with rare exceptions, is failure of the hypertrophied heart, has been frequently demonstrated,¹⁻⁸ and is now widely accepted.⁹⁻¹³ In the absence of deforming valvular disease, congenital cardiac defects, mechanical barriers in the pulmonary circulation, adherent pericardium, or diffuse inflammatory myocardial disease, cardiac hypertrophy is generally referred to systemic arterial hypertension. When there exists a reliable clinical record of elevated blood pressure, this opinion appears to be valid. May, however, the rôle of antecedent hypertension be invoked when it is not clinically apparent? Because the blood pressure in patients with essential hypertension may be permanently reduced as a result of myocardial infarction,¹⁴ or undergo alterations of a spontaneous nature^{10, 15} or as a result of congestive heart failure,^{10, 15} normal values obtained during the course of clinical observation cannot be used to exclude the possibility of antecedent hypertension.

In the absence of clinically demonstrated hypertension in cases of congestive heart failure with myocardial hypertrophy, may morphologic evidence be used to determine the presence or absence of antecedent hypertension? Although myocardial hypertrophy, without obvious cause, is in itself often interpreted as evidence that hypertension existed during life,^{5, 6, 10, 16-18} proof for this is lacking. Alterations in the arterioles, particularly those of the kidneys, have been the commonly utilized structural indication of the existence of hypertension. Their use for this purpose has limitations because of the uncertainty concerning their incidence. It is held by many,^{15, 16, 19-24} and denied by others,²⁵⁻²⁷ that sclerosis of the arterioles is a constant feature of essential hypertension. The problem is further complicated by the occasional occurrence of arteriolar sclerosis in apparently normal non-hypertensive individuals, and in them bears some relationship to age.^{15, 19, 28-30}

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During a period of three years, 43 cases of congestive heart failure with predominant left ventricular hypertrophy of uncertain etiology have come to necropsy from the wards of the Third (New York University) Division of Bellevue Hospital. Valvular disease, congenital defects, syphilitic aortitis, adherent pericardium, and inflammatory myocardial disease were absent, and the available blood pressure readings were normal. It occurred to us that if antecedent systemic arterial hypertension played a significant rôle in the cardiac hypertrophy of these patients, they should exhibit an incidence of arteriolar sclerosis similar to that observed in known cases of essential hypertension, and considerably above that of nonhypertensive individuals of the same age period. This report represents a comparative study designed to test this proposition and embraces a consideration of other factors which might operate in the pathogenesis of cardiac hypertrophy.

SOURCES OF MATERIAL AND METHODS

The cases employed in this study represent successive necropsies during a three-year period, excluding patients with valvular disease of the heart, congenital cardiac defects, syphilitic aortitis, adherent pericardium, inflammatory myocardial disease, or cor pulmonale. All of the necropsies were performed or supervised by one or more of us, and the method of examination was constant. The hearts were detached from the ascending aorta from 3 to 5 cm. above the aortic ring, and weighed unfixed, devoid of blood or parietal pericardium. The coronary arteries were opened throughout their subepicardial course by coronary scissors, or by transverse serial sections at intervals of 3 to 4 mm., or both.

The vessels of the kidneys and adrenals were chosen for microscopic study. A minimum of two, and an average of four, sections of each organ, stained with hematoxylin and eosin after paraffin embedding, were studied. The sections were mixed, and examination was made and recorded without knowledge of the clinical history or of the necropsy findings.

The spleen was not utilized because physiologic arteriolar changes in this organ are extremely common. The pancreas was excluded because autolysis often produces alterations in the arterioles simulating arteriolar sclerosis. Other viscera show the lesion too infrequently to be useful in this study.

In the kidney sections the preglomerular arterioles were studied for evidence of subendothelial hyaline thickening, which was classified as severe when the majority were involved, as mild if 2 to 5 affected arterioles were found in a single section, as 1+ if only a single hyalinized arteriole was discovered in any section, and as absent if none was

TABLE I
RENAL AND ADRENAL ARTERIOLAR SCLEROSIS IN 269 NONHYPERTENSIVE SUBJECTS

DECADE	NO. OF CASES EXAMINED	PRESENT IN SOME DEGREE IN KIDNEYS OR ADRENALS		PRESENT AS 1+ IN KIDNEYS		PRESENT AS MILD OR SEVERE IN KIDNEYS		PRESENT AS MILD OR SEVERE IN ADRENALS		PRESENT AS MILD OR SEVERE IN KIDNEYS OR ADRENALS		ARTERIAL SCLEROSIS OF KIDNEYS	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
3	22	1	4.5	1	4.5	0	0	0	0	0	0	0	0
4	39	6	15.5	3	7.8	2	5.1	3	7.8	3	7.8	3	7.8
5	58	17	29.3	11	18.9	4	6.9	6	10.3	8	13.7	12	20.6
6	70	24	34.3	12	17.1	9	12.8	10	14.2	13	18.5	27	38.5
7	44	20	45.4	12	27.2	5	11.3	12	27.2	14	31.8	21	47.7
8	29	17	58.6	4	13.7	11	37.9	8	27.5	14	48.2	20	68.9
9	7	4	57.1	1	14.2	3	42.8	2	28.5	3	42.8	5	71.4

encountered. Sclerosis of the interlobular and arcuate arteries was recorded as mild or severe, depending on the diffuseness of the lesion and the degree of reduction of the lumen. Alterations of the arterioles in the capsule or pericapsular areolar tissue of the adrenals were noted as mild or severe, corresponding to the diffuseness of subendothelial hyaline thickening.

Clinical data were obtained from the hospital charts and recorded without knowledge of the necropsy findings. The diagnosis of congestive heart failure was made on clinical evidence.³¹

INCIDENCE OF ARTERIOLAR SCLEROSIS IN NONHYPERTENSIVE SUBJECTS

This group comprises 269 cases in which there was no clinical evidence of heart disease, chronic anemia, or hyperthyroidism, and in which the systolic blood pressure was constantly below 150, and the diastolic below 90. The incidence of sclerosis of the arterioles and arteries increases with advancing age (Table I), mild or marked sclerosis of the renal arteries is from two to four times as common as comparable degrees of sclerosis of the afferent glomerular arterioles, and the latter vessels are affected in mild or severe degree with increasing frequency, reaching an incidence of 42.8 per cent in the ninth decade. The adrenal arterioles are involved slightly more frequently than the renal arterioles.

In this group the incidence of 1+ renal arteriolar sclerosis shows little variation with age and is similar to that observed in the groups to be described subsequently. This constancy indicates that such sparse alterations have no relationship either to age or hypertension and therefore are of no value. Moritz and Oldt³⁰ observed similar focal vascular alterations in various tissues but disregarded them in their classification of the severity of arteriolar sclerosis.

With the possibility in mind that those patients with mild or severe arteriolar disease might have had essential hypertension before they were observed clinically, their cardiac weights were studied. The average weight of the hearts in the 55 cases in which there was mild or severe renal or adrenal arteriolar sclerosis was computed and found to be 336 gm. for males and 300 gm. for females. Similar average weights were obtained in the 34 cases in which there was mild or severe sclerosis of the renal arterioles alone. These results agree essentially with the average heart weights for the group as a whole (327 gm. for males and 279 gm. for females). Further evidence that the alterations in the arterioles of the kidneys and adrenals in this group were not the result of arterial hypertension is found in the fact that in only 7 of the 55 cases of this group did the heart weight exceed 400 gm. for males and 350 gm. for females.

INCIDENCE OF ARTERIOLAR SCLEROSIS IN ESSENTIAL HYPERTENSION

This group consists of 154 cases of hypertension, with a systolic blood pressure above 150, and a diastolic blood pressure above 90. All instances of chronic glomerulonephritis, hydronephrosis, chronic pyelonephritis, and polycystic kidneys were excluded.

There were 96 males and 58 females. Table II reveals the distribution of these cases according to the cause of death. Congestive heart failure was the cause of death in 63, or 40.9 per cent. In 10 additional cases congestive heart failure occurred during the period of clinical observation, although it was not the primary cause of death.

TABLE II
CAUSE OF DEATH IN 154 CASES OF ESSENTIAL HYPERTENSION

CAUSE	NO. OF CASES	PER CENT
Congestive heart failure*	63	40.9
Coronary thrombosis with shock	2	1.3
Cerebral hemorrhage and cerebral arteriosclerosis	28	18.1
Uremia	13	8.4
Hypertensive encephalopathy	7	4.5
Acute infections	16	10.4
Others	25	16.2

*Includes 15 cases of coronary thrombosis.

In these 154 cases the average weight of the heart was 537 gm. for males and 455 gm. for females. In the 73 cases of congestive heart failure the average heart weight was 613 gm. for males and 463 gm. for females, contrasting with that of 461 gm. for males and 450 gm. for females who did not show congestive heart failure.

The incidence of arterial and arteriolar sclerosis in 144 cases of essential hypertension is recorded in Table III. The group has been subdivided to illustrate the differences between those patients who died of congestive heart failure (69 cases) and those in whom congestive heart failure, cerebral arterial disease, and uremia were absent (33 cases). This division was made in order to compare the incidence of arteriolar changes in patients who died in the end stage of their disease (congestive heart failure, uremia, cerebral vascular disease) and in those who died prematurely of unrelated causes, in whom the vascular alterations might have been aborted. Of the former, 57, or 82.5 per cent, showed moderate or severe renal arteriolar sclerosis, contrasted with 18, or 54.6 per cent, of the latter group.

INCIDENCE OF ARTERIOLAR SCLEROSIS IN CARDIAC HYPERTROPHY
OF UNCERTAIN ETIOLOGY

Included in this group are 43 patients with congestive heart failure whose blood pressure did not exceed 150 systolic and 90 diastolic. In all but two, congestive heart failure was present at the time of death.

TABLE III
RENAL AND ADRENAL ARTERIOLEAR SCLEROSIS IN 144 CASES OF ESSENTIAL HYPERTENSION

GROUP	PRESENT IN SOME DEGREE IN KIDNEYS OR ADRENALS		PRESENT AS 1+ IN KIDNEYS		PRESENT AS MILD OR SEVERE IN KIDNEYS		PRESENT AS MILD OR SEVERE IN ADRENALS		PRESENT AS MILD OR SEVERE IN KIDNEYS OR ADRENALS		ARTERIAL SCLEROSIS OF KIDNEYS	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Entire group of 144 cases	126	87.5	21	14.6	102	71.0	93	64.5	113	78.5	121	84.0
69 cases with C.H.F.*	66	95.8	8	11.6	57	82.5	53	79.7	63	91.4	66	95.8
33 cases not dying of C.H.F., C.A.,† uremia or hyp. enc.‡	25	75.8	7	21.2	18	54.6	13	39.4	22	66.7	21	63.6

*Congestive heart failure.

†Cerebral arteriosclerosis or hemorrhage.

‡Hypertensive encephalopathy.

Valvular deformities, congenital cardiac defects, adherent pericardium, syphilitic aortitis, and inflammatory myocardial disease were absent in this group as in the two preceding groups. The age and sex of these patients are recorded in Table IV.

TABLE IV

AGE AND SEX IN CASES OF MYOCARDIAL HYPERTROPHY OF UNCERTAIN ETIOLOGY

DECADE	MALES	FEMALES
3	0	1
4	2	0
5	4	2
6	8	1
7	14	1
8	6	2
9	2	0
Total	36	7
Ratio	5.1	1

The anatomical diagnosis of cardiac hypertrophy is based in 32 instances upon heart weight in excess of 400 gm. for males and 350 gm. for females in patients whose body weight did not exceed 170 lb. In 3 instances, though the weight of the heart was below 400 gm., it was considered hypertrophied in relation to body weight. In those patients who weighed more than 170 lb., the heart weight was 450 gm. or more (8 cases). The heart weights are charted in Table V and are compared with those of patients with essential hypertension who died of congestive heart failure. The average heart weight for the undetermined etiology group (males 520 gm., females 460 gm) is below that of the hypertensive group (males 613 gm., females 463 gm.).

TABLE V

HEART WEIGHT IN CASES OF CONGESTIVE HEART FAILURE AND MYOCARDIAL HYPERTROPHY

HEART WEIGHT	UNCERTAIN ETIOLOGY		HYPERTENSIVE	
	MALE	FEMALE	MALE	FEMALE
300-349		1		3
350-399	1	1		8
400-449	6	2	5	
450-499	9		3	5
500-549	6	2	5	5
550-599	5		4	1
600-649	6	1	14	4
650-699	1		4	1
700-749	2		6	
750-799			3	1
800-849			1	
850-899			1	
900-940			2	
Total	36	7	48	28
Average heart weight	520	460	613	463

Table VI illustrates the incidence of arterial and arteriolar sclerosis and, when compared with Table III, shows the differences between these patients and those with essential hypertension. Mild or severe sclerosis of the renal arterioles is less than half as frequent in this group (30.9 per cent) as in cases of essential hypertension with congestive heart failure (82.5 per cent). A similar difference is observed when the incidence of mild or severe renal and adrenal arteriolar sclerosis is compared in the two groups (45.3 per cent and 91.4 per cent, respectively). Fig. 1 illustrates the distribution by decades of arteriolar sclerosis of the kidneys in this group as compared with the foregoing groups.

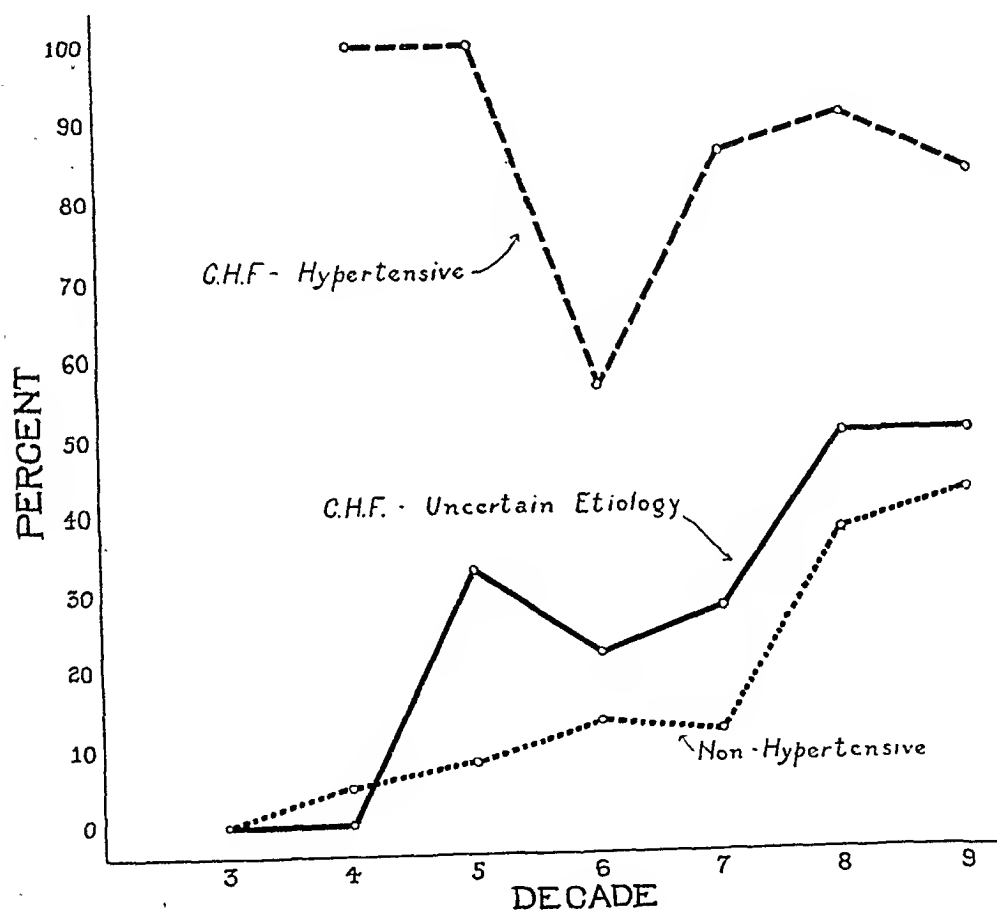


Fig. 1.—Relation of mild or severe renal arteriolar sclerosis to age. C. H. F., congestive heart failure.

ANALYSIS OF DATA

It has been shown that mild or severe renal arteriolar sclerosis occurs in 12.6 per cent of nonhypertensive individuals and that in them its occurrence bears a definite relationship to age. These findings agree with those of Moritz and Oldt.³⁰ It is evident that subendothelial hyalinization of the renal arterioles in certain instances represents a senescent degenerative process which does not require for its production an abnormally elevated systemic arterial blood pressure.

TABLE VI

RENAL AND ADRENAL ARTERIOLAR SCLEROSIS IN 42 CASES OF MYOCARDIAL HYPERTROPHY OF UNCERTAIN ETIOLOGY

GROUP	PRESENT IN SOME DEGREE IN KIDNEYS OR ADRENALS		PRESENT AS 1+ IN KIDNEYS		PRESENT AS MILD OR SEVERE IN KIDNEYS		PRESENT AS MILD OR SEVERE IN ADRENALS		PRESENT AS MILD OR SEVERE IN KIDNEYS OR ADRENALS		ARTERIAL SCLEROSIS OF KIDNEYS	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Entire group of 42 cases	23	54.7	6	14.2	13	30.9	13	30.9	19	45.3	26	61.8
18 cases of myocardial infarction	12	66.7	3	16.6	7	38.9	8	44.4	10	55.6	13	72.3
24 remaining cases	11	45.8	3	12.4	6	25.0	5	20.8	9	37.5	13	54.2

The question of the constancy of arteriolar sclerosis in essential hypertension has played an important rôle in the search for the pathogenesis of that condition. Moritz and Oldt³⁰ found renal arteriolar sclerosis of significant degree in 97 of 100 cases of chronic hypertension and concluded "that renal arteriolar sclerosis is the most common cause of chronic hypertension." We encountered significant renal arteriolar sclerosis in 102 of 144 cases of essential hypertension, but, whereas Moritz and Oldt limited their study to patients with chronic hypertension dying in the end stage of the disease, our material included patients with hypertension in whom the natural course of the disease was interrupted by fatal intercurrent illness. That this variation in choice of material may be significant is revealed by the differences observed in the incidence of renal arteriolar sclerosis in our cases when a similar division is made. Arteriolar sclerosis was present in the kidneys of 82.5 per cent of patients with hypertension who died of congestive heart failure but was found in only 54.6 per cent of those who did not show evidence of congestive heart failure, uremia, or cerebral vascular disease.

The investigation of renal arteriolar sclerosis herein reported was designed to ascertain whether this vascular lesion could be utilized as a morphologic index of the existence of systemic arterial hypertension. Consideration of the pathogenesis of essential hypertension was not within the purpose of this study. The absence of subendothelial hyaline thickening of the renal arterioles in 45.5 per cent of cases of essential hypertension in which death occurred before the natural termination of the disease does not necessarily invalidate the rôle of renal ischemia in the genesis of chronic hypertension.³⁴ Of the 42 cases of essential hypertension in which there was no significant renal arteriolar sclerosis, sclerosis of the arcuate or interlobular arteries was found in 24. It is felt that in the remaining 18 cases the existence of

renal isehemia due to localized sclerosis of the larger branches of the renal arteries or their ostia cannot be excluded because of the limitations of examination.

As was pointed out earlier in this report, it was believed that, if arterial hypertension played a major rôle in the genesis of cardiac hypertrophy in the patients of the uncertain etiology group, then the incidence of renal arteriolar sclerosis in this group should be similar to that observed in known cases of essential hypertension. In the material analyzed, renal arteriolar sclerosis occurred in 82.5 per cent of patients with essential hypertension who died with congestive heart failure, but in only 30.9 per cent of those in the group of uncertain etiology. The age distribution of renal arteriolar sclerosis in the latter group is similar to that observed in nonhypertensive individuals (Fig. 1). Since a correlation exists between group incidence of sclerosis of the renal arterioles and chronic hypertension, the divergent frequency of this vascular lesion in these two groups suggests that they are also different in respect to the existence of arterial hypertension. Hence the deduction appears to be valid that hypertension did not play the same rôle in the cardiac hypertrophy of patients in the group of uncertain etiology as it did in the patients with essential hypertension. In respect to heart weight and sex distribution there are additional points of difference between the two groups (Table V).

It appears that there are no characteristics in common in these cases to permit identification as a unified group. Hence an effort was made to analyze further those factors which might operate in the production of cardiac hypertrophy.

FACTOR OF CORONARY SCLEROSIS

That coronary sclerosis may play a rôle in cardiac hypertrophy has been asserted by some^{2, 9, 36, 37} and denied by others.^{3, 5, 16, 35} The degree of coronary sclerosis was determined in the group of patients with cardiac hypertrophy of uncertain etiology and graded as + if there was atherosclerosis without reduction in the lumen, as ++ if there was slight reduction in the lumen, and as +++ if there was partial or complete occlusion of the lumen because of atherosclerosis or thrombosis.

In 19, or 44.2 per cent of the cases of uncertain etiology, coronary sclerosis was absent or recorded as + and cannot be considered as a factor in the production of myocardial hypertrophy, for this degree of coronary sclerosis is almost constant in persons in the fifth and later decades of life who exhibit neither clinical nor necropsy evidence of heart disease. In the remaining 24 cases (55.8 per cent), there was ++ or +++ coronary sclerosis, but, since myocardial infarction was present in 16 of these, coronary sclerosis per se could have played a

rôle in myocardial hypertrophy in only 8. In 4 of the latter other factors demand consideration (Table VII).

TABLE VII

POSSIBLE ETIOLOGIC FACTORS IN 43 CASES OF CARDIAC HYPERTROPHY OF UNCERTAIN ETIOLOGY

FACTOR	NO. OF CASES	MILD OR SEVERE RENAL ARTERIO-LAR SCLEROSIS		AVERAGE HEART WEIGHT		CORONARY SCLEROSIS NO. OF CASES	
		NO.	%	MALE	FEMALE	NONE OR +	++ OR +++
Myocardial infarct	18	7	38.9	536	340*	2	16
Auricular fibrillation	5	0		556	510*	4	1
Chronic anemia	2	0		435		1	1
Hyperthyroidism	2	1	50.0		510	1	1
Combination of anemia and infarct	1	1	100.0	590			1
Unknown	15	4	26.6	494	450†	11	4

*1 case

†3 cases

FACTOR OF MYOCARDIAL INFARCTION

Old or both old and recent myocardial infarcts were present in 18 cases of cardiac hypertrophy of uncertain etiology. That myocardial infarction may lead to cardiac hypertrophy has been asserted by many.^{2, 6, 9, 17, 38, 39} However, that hypertrophy frequently does not appear following infarction of the myocardium has been our experience as well as that of Horine and Weiss.²⁰ In the period encompassed by this study, 11 instances of old organized myocardial infarcts in hearts of normal size were encountered.

Although it is clear that infarction of itself does not constantly result in cardiac hypertrophy, infarction which leads to cardiac dilatation may produce it.^{12, 32, 37} However, the following consideration supports the view that many of the cases of myocardial infarction in the group of cardiac hypertrophy of uncertain etiology represent instances of antecedent hypertension. Renal arteriolar sclerosis of mild or severe degree was found in 7 of the 18 cases (Table VI), an incidence which is only slightly less than that found in a group of cases of known hypertension with myocardial infarction (10 of 20 cases).

It is thus apparent that, although some of the cases of myocardial infarction in this group represent instances of antecedent hypertension, the actual number of these is not determinable.

OTHER POSSIBLE ETIOLOGIC FACTORS

If the 18 cases of myocardial infarction are excluded from the group of uncertain etiology, there are 25 instances in which the cause of

myocardial hypertrophy remains to be established. Considered as a group, the possible rôle of antecedent hypertension finds little morphologic support, for mild or severe renal arteriolar sclerosis was present in only 6, or 25 per cent (Table VI), and all of these patients were in the seventh and eighth decades, a period in which there is a not uncommon natural occurrence of these vascular changes (Table I). The average heart weight in this group (506 gm. for males and 480 gm. for females) was also somewhat below that which obtained in the hypertensive group. Significant degrees of coronary sclerosis occurred in only 8, or 32 per cent. Myocardial lesions of inflammatory nature were not found, and fibrosis of the myocardium was absent or of insignificant degree.

In Table VII the group of uncertain etiology has been subdivided according to various factors which, either in themselves or in association with others, might have played a rôle in the genesis of hypertrophy.

There were 5 cases in which protracted auricular fibrillation might have contributed to the development of myocardial hypertrophy. Renal arteriolar sclerosis was absent in all, and in only 1 instance could significant coronary disease be invoked as an additional factor. In 1 case the known duration of this arrhythmia was thirteen years, in another it was ten years, and in a third it was five years. In the study reported by Brown⁴⁰ there were 9 cases of persistent auricular fibrillation and cardiac hypertrophy.

Evidence that chronic anemia may lead to cardiac hypertrophy has been advanced by several investigators.⁴¹⁻⁴⁴ There were two patients with chronic anemia in this group; neither had arteriolar lesions, but one had coronary sclerosis. Cardiac hypertrophy was slight (420 and 450 gm.), and may have been related to the existing anemia.

Hyperthyroidism was prominent in 2 cases of this group, and in 1 case it was of six years' duration. Mild renal arteriolar sclerosis and ++ coronary sclerosis was present in 1 case.

In 1 case the association of severe chronic anemia, myocardial infarction, and mild renal arteriolar sclerosis precludes the implication of any one factor.

There remain 15 cases in this group of uncertain etiology in which none of the above factors existed. The low incidence of renal arteriolar sclerosis and the comparatively slight degree of cardiac hypertrophy separate this group from that of essential hypertension with congestive heart failure. A significant degree of coronary narrowing occurred in 4 of these cases and might have played a rôle in cardiac hypertrophy.

Although it is conceded that myocardial hypertrophy may have been the result of congestive heart failure in these cases, the nature of

any myocardial defect which might have reduced the efficiency of the heart is obscure. No structural myocardial alteration which might have initiated this process has been demonstrated in these 15 cases. The myocardial lesions disclosed by histologic study are of no apparent significance; they were small, scattered, interstitial, fibrous foci similar to those encountered in any hypertrophied heart. Since it is believed that vitamin B deficiency may be related to congestive heart failure,^{45, 46} the clinical records in these cases were examined for possible evidence of the existence of vitamin B deficiency, but none was found.

Levy and von Glahn⁴⁷ recently reported 10 patients with congestive heart failure in whom cardiac hypertrophy of obscure cause existed. Some of their cases are similar to those in our group in respect to the absence of significant myocardial alterations.

Finally, it must be admitted that there may have been one or several unknown morphologic or functional abnormalities which helped to produce cardiac hypertrophy in these cases. Although the rôle of antecedent hypertension cannot be excluded in the individual case, its absence in the majority of these cases appears probable. Until further evidence is forthcoming, such clinical terms as "hypertrophy due to previous hypertension" or "arteriosclerotic heart disease" in designation of such cases should be employed with caution.

SUMMARY

Forty-three cases of preponderant left ventricular hypertrophy of uncertain etiology, associated with congestive heart failure, have been analyzed. Valvular disease, congenital cardiac defects, syphilitic aortitis, adherent pericardium, and inflammatory myocardial disease were excluded, and the available blood pressure readings were normal.

The possible rôle of antecedent hypertension in the genesis of cardiac hypertrophy was tested by comparing the incidence of renal arteriolar sclerosis in this group of patients with that in 269 nonhypertensive subjects of similar age and in 69 patients with essential hypertension who died in congestive heart failure.

Renal arteriolar sclerosis occurred in 12.6 per cent of nonhypertensive patients and in them bears a relation to age. In patients with chronic hypertension who died in congestive heart failure, sclerosis of the renal arterioles was encountered in 82.5 per cent, whereas in 42 cases of cardiac hypertrophy of uncertain etiology the incidence of this lesion was only 30.9 per cent.

Evidence is presented which suggests that antecedent hypertension played a part in the development of cardiac hypertrophy in many of the 18 cases of myocardial infarction which are included in this group. Other possible factors in the cardiac hypertrophy, namely, coronary

sclerosis, protracted auricular fibrillation, chronic anemia, and hyperthyroidism, were found in 14 of the 43 cases of uncertain etiology. In the remaining 11, structural or functional abnormalities which might have initiated cardiac dilatation and hypertrophy were not apparent. It is felt that although the rôle of antecedent hypertension cannot be excluded in the individual case, its absence in the majority of these cases appears probable.

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ABNORMAL DISTRIBUTION OF THE SUPERFICIAL MUSCLE BUNDLES IN THE HUMAN HEART*

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IT HAS often been remarked that knowledge is incomplete until quantitative data are available. Thus, information regarding the human coronary artery distribution acquired more practical value when Spalteholz¹ and later Gross² and Barnes and Whitten³ were able to show that in 80 per cent of hearts one type of distribution was found. In regard to the ventricular muscle bands certain questions have come to mind:

1. Are these muscle bands present in all human hearts?
2. Are they present in an entirely constant pattern in all human hearts?
3. Are they present in a recognizable pattern but in relatively different masses under certain conditions?
4. What physiologic implications are involved in answering the above questions?

Constancy of Presence.—The first question is easily answered. Among fifty human hearts dissected in this laboratory, *none* has been found in which the superficial and deep sinospirals and bulbospirals were not identifiable. This is in accord with the observations of previous investigators (see Robb⁴ for bibliography comprising 65 references), none of whom mention ever having studied a heart in which the discrete ventricular muscle bands were absent. The conclusion is warranted that the individual ventricular muscle bands are identifiable in 100 per cent of cases.

Constancy of Pattern.—a. The constancy of the pattern in all human hearts is another matter, though there is a general similarity. Thus far, no heart has been examined by us which did not have a *superficial bulbospiral muscle* arising from some part of the left auriculoventricular ring and spiraling downward to the apex to penetrate and form the inferior (posterior) papillary muscle. The variability of pattern in this muscle is observed chiefly in the extent of its origin. In some cases there may be an origin from the auriculoventricular ring at the right side of the pulmonary artery. MacCallum⁵ (p. 312, Figs. 3 and 16) considers the origin of this layer to be "almost entirely from the tendon of the conus." Mall⁶ describes the origin as from "the conus, the left side of the aorta, and the left side of the left auriculoventricular ring" (Mall,⁶ p. 219, Fig. 1A-A'). Fibers of origin from the aorta and the

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left side of the left auriculoventricular ring were found in 100 per cent of our specimens. In about 20 per cent there is no origin further to the right, and in less than 10 per cent of hearts does a portion of the superficial bulbospiral muscle extend completely around the conus to its tendon. The posterior border of the origin of this muscle in about 5 per cent of the cases is at the obtuse margin. In 80 to 90 per cent it is at the mid-point of the posterior curve of the left auriculoventricular ring, and in 5 per cent (or less) a few fibers attach to the posterior end of the ligament. The portion of the inferior (posterior or diaphragmatic) surface of the heart which is covered by this muscle varies with the extent of the posterior origin. It may cover the apical two-thirds of the left ventricle and one-third of the right (if the origin ends at the obtuse margin), or as much as the whole of the left ventricle and the apical half of the right if the fibers attach to the whole posterior curve of the left auriculoventricular ring. There is some variability in the width of the band which curves about to form the posterior horn at the apex (Mall,⁶ Fig. 7 C, p. 237).

b. A *superficial sinospiral* muscle is present in all hearts examined. The origin of this muscle is also somewhat variable. In about 5 per cent of the hearts the origin may extend from the entire posterior curve of the left auriculoventricular ring as far as the obtuse margin; in 80 to 90 per cent it will reach only to the mid-point of the left posterior curve of the left auriculoventricular ring, and in another 5 per cent of cases will have its entire origin from the right auriculoventricular ring. According to the extent of the origin, this muscle may cover the basal (upper) third of the left ventricle posteriorly, or may be confined entirely to the basal portion of the right ventricle. Even more important than the posterior extent of origin of this muscle is its variability on the anterior surface of the heart. At present it seems statistically unjustifiable to place much stress upon the percentage of variability in the anterior inferior portion of this muscle, for these specimens are not random samples, but are mainly hearts known to be abnormal and, moreover, the variations are manifold. Among 50 hearts examined, 4 showed great variation in pattern. Fig. 1 portrays the typical sweep of the superficial sinospiral fibers downward and forward over the anterior wall of the right ventricle. They cross the anterior interventricular sulcus, where the band condenses to form the lower third (or less) of the anterior wall of the left ventricle and the anterior horn at the apex, and then penetrates to form the anterior papillary muscle. Fig. 2 shows how the direction of these fibers is altered from an oblique to an almost horizontal direction by a considerable degree of cardiac hypertrophy, predominantly left-sided. Figs. 3 and 4 show deficiencies in this layer with abnormal insertion under the superficial bulbospiral and lessened participation in the formation of the anterior horn and anterior papillary muscle. Where the superficial sinospiral is deficient in the apical

region, the deep sinospiral emerges from the septum and becomes part of the anterior surface and contributes to the anterior horn and the anterior papillary muscle. In the light of Bremer's description⁷ of the formation of the ventricles as "aneurysmal out-pouchings," such alterations in surface pattern are explicable.

c. The *deep sinospiral* muscle is fairly constant in pattern. It is deficient in the presence of large ventricular septal defects and may appear at the surface or contribute to the anterior horn and anterior papillary muscle as described above.

d. No variation in pattern of the *deep bulbospiral* muscle has been noted in this laboratory. Mall described this muscle as forming a cuff about the base of the left ventricle and passing through the septum,

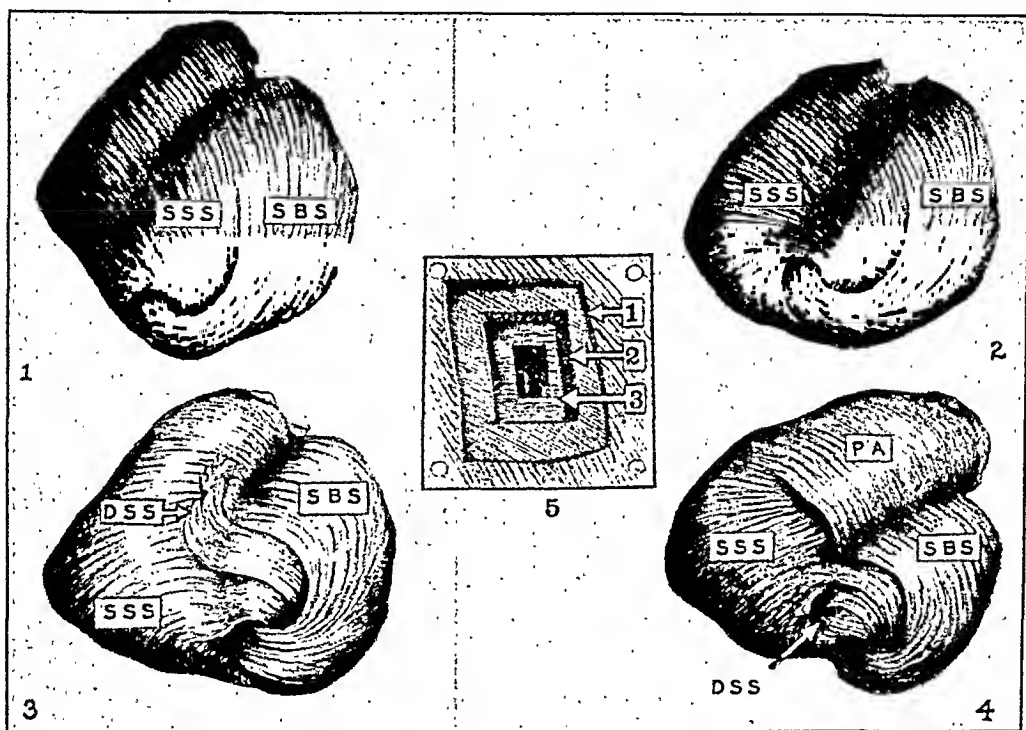


PLATE I.—Variations of superficial musculature in human hearts. (Anterior aspect, $\times \frac{1}{2}$.) Figs. 1-4 show anterior foreshortening due to tilting up of apex to exhibit the vortex. SSS. = superficial sinospiral muscle; SBS. = superficial bulbospiral; DSS. = deep sinospiral muscle; PA. = conus of pulmonary artery.

Fig. 1.—Normal, note oblique direction of SSS fibers.

Fig. 2.—Hypertrophy with more horizontal course of SSS. fibers.

Figs. 3 and 4 depict abnormal evagination of the deep sinospiral muscle fibers to the surface.

Fig. 5.—Window cut in lateral wall of left ventricle at the base showing relative thickness of muscle layers: arrows 1 = SBS, 2 = DSS, and 3 = DSS muscles, each layer characterized by different fiber direction (see Mall⁶).

but he did not emphasize the fact that it also encircled the aorta (Mall,⁶ Figs. 9 and 11). Shaner^{8c} finds that the deep bulbospiral surrounds both the aorta and the mitral orifice. This observation we have confirmed in human hearts.

Relation of Mass to Function.—Since these ventricular muscle bands are always present, we may inquire whether each has a specific function. W. G. MacCallum⁹ writes (p. 451): "The arrangement of the musculature of the heart walls (J. B. MacCallum, Mall) is such as to control

TABLE I

LESION	THICKNESS IN MM. OF RIGHT VENTRICULAR WALL					THICKNESS IN MM. OF LEFT VENTRICULAR WALL						
	SSS	DSS	TOTAL	% TOTAL		SBS	DSS	DBS	TOTAL	% TOTAL		
				SSS	DSS					SSS	DBS	DSS
Normal*	1	3	4	25.0	75.0	1	3	6	10	10	30	60
1. Heart of small female. Normal valves, Coronary sclerosis.	0.75	2.25	3.0	25.0	75.0	1	2	4	7	14.5	29	57
2. Hypertrophy with hypertension. Valves normal.	1	3	4	25.0	75.0	1	6	9	16	7	37	56
3. Hypertension. Coronary sclerosis, Left ventricular hypertrophy.	1	3	4	25.0	75.0	1	5	15	25	4	20	76
4. Aortic stenosis.	1	4	5	20.0	80.0	1	5	11	17	6	29	65
5. Hypertension. Mitral stenosis, Coronary sclerosis, Old apical infarct.	1	6	7	14.5	85.5	1	3	13	17	6	18	76
6. Early mitral.	1	7	8	12.5	87.5	1	3	7	11	9	27	64
7. Moderate mitral stenosis + re- gurgitation. Moderate aortic stenosis + re- gurgitation. Early tricuspid.	1	8	9	11.1	88.9	1	3	9	13	8	23	69
8. Buttonhole mitral. Tricuspid regurgitation. Aortic stiffening.	1	6	7	14.3	85.7	1	3	3	7	14	43	43

*The figure of 4 mm. for the right ventricular wall and of 10 mm. for the left agrees with the upper limit of normals, without trabeculae, established by Nauwerck (quoted by Mallory and Wright¹¹).

with greatest completeness the propulsion of blood; not only does it obliterate the cavity of the ventricles, but by the contraction of the papillary muscles it insures the proper tension and perfect closure of the auriculo-ventricular valves. Further, special subdivisions of the muscle support the semilunar valves and maintain their closure in such a way that even with slight imperfections of the valve leakage is much diminished by this muscular action."

This concept has been tested experimentally (Robb, Hiss, and Robb¹⁰). In brief, the two superficial muscles are responsible for little else than the fixing of the auriculoventricular valve leaflets during ventricular systole. Experimental injury has scarcely any effect on blood pressure. When the deep sinospiral contracts, it lessens all transverse diameters of the heart. It does all of the work of the right ventricle, and some of that of the left. Experimental injury will lower the blood pressure considerably, perhaps to half of its original value. The deep bulbo-spiral is responsible for the final emptying of the left ventricle and maintains systemic blood pressure at the end of systole. When this muscle relaxes, the aortic valves close. Experimental injury to this muscle causes a tremendous fall of blood pressure and often sudden death. If these experimentally observed functions prevail during life, various chronic lesions should lead to differential hypertrophy. Table I gives the measurements of the cross section of the muscles in the ventricular walls under various conditions, and Fig. 5 presents a sketch illustrating the method of obtaining the information.

It is readily seen (Table I) that in mitral disease the right portion of the deep sinospiral is hypertrophied. Normally this muscle comprises 75 per cent of the right ventricular wall. In mitral disease (e.g., Cases 5, 6, 7, 8) it formed 85 per cent, 87 per cent, 89 per cent and 86 per cent, respectively.

Normally the deep sinospiral forms about 30 per cent of the left ventricular wall at the base. In Case 2, showing general cardiac hypertrophy, this muscle increased its relative thickness to 37 per cent. Moreover, in a small heart (Case 8), in which both aortic and severe mitral disease were present, this muscle formed 43 per cent of the wall. When the work of the left ventricle is considerably increased, as in hypertension with hypertrophy (Case 3) and aortic stenosis (Case 4), the percentage of its mass was unchanged or even decreased though actually the muscle was thickened.

The deep bulbo-spiral normally forms about 60 per cent of the left lateral ventricular wall at the base. It is interesting to note that in Cases 3 and 5, in which hypertension was present, this muscle formed 76 per cent of the wall. In early uncomplicated mitral disease (Case 6) the deep bulbo-spiral was not significantly altered (normally 60 per cent of left wall, here 64 per cent), although the deep sinospiral on the right had increased in this heart from the normal of 75 to 87 per cent. In

a very small heart (Case 8) with very high-grade mitral disease, the deep bulbospiral formed less of the left wall than is normal and the deep sinospiral hypertrophied to 86 per cent on the right and 43 per cent on the left. Presumably in this case very inadequate filling of the left ventricle occurred, thus reducing the demand on the left ventricle. Variability in the deep bulbospiral was previously noted by Mall⁶ (p. 247): "In the newborn and in young children this band is very insignificant, which indicates that during growth it must enlarge faster than the other heart muscle bundles. It also varies in size in the adult heart. Figs. 5 to 12 are taken from an hypertrophied heart which shows the circular bands markedly thickened. On the other hand, in a dilated heart with thin walls it is barely present, as Fig. 13 shows. To show further variations I add an illustration of a well-developed small heart in Fig. 14. Here the deep bulbospiral band is unusually well-developed, in fact as well as in the hypertrophied heart shown in Figs. 5 to 12."

In no instance of either hypertrophy or valvular lesion was there a measurable change in thickness of the surface layers of the superficial muscles. When mitral disease was advanced, the right papillary muscles tended to hypertrophy. In the most severe mitral lesion (Case 8), with reduction of the orifice to a small slit measuring only 7 by 1 mm. and calcification of the fused valve leaflets, the papillary muscles were atrophied. In the hypertensive hearts, and especially in the presence of aortic stenosis, the left papillary muscles were hypertrophied.

These findings substantiate the experimental conclusions regarding function. There is no doubt that differential hypertrophy of the ventricular muscle bands can and does occur in human hearts.

Physiological Implications.—Differences in surface pattern of the ventricular muscles offer a heretofore-unmentioned possibility of explaining the variable results of timing of initial negativity, of analyzing, localizing, and studying the contour of premature systoles, and of learning about the injury which may be inflicted by surgical exploration of the heart. It follows that if data are presented dealing with surface localization, an accurate sketch of the muscle arrangement should be provided (the fat and epicardium being first removed).

SUMMARY AND CONCLUSIONS

1. Fifty human hearts have been dissected to demonstrate the ventricular muscle bands.

2. The superficial and deep sinospiral and bulbospiral muscles were present in all hearts. We know of no report in which these muscles were said to be absent.

3. The surface pattern of these muscles, especially at the lower anterior surface of the right ventricle, at the right ventricle near the conus, along the trabeculated area, and at the anterior horn of the left

ventricle, is variable. The angle at which the superficial sinospiral muscle fibers pass from the anterior horn to the right base varies considerably. In small hearts the fibers have an oblique course, tending to approach the vertical from apex to base. In hypertrophied hearts these fibers have an almost horizontal course.

4. The masses vary considerably. The right portion of the deep sinospiral is differentially hypertrophied in mitral disease or in any other disease characterized by increased resistance to pulmonary blood flow. The deep bulbospiral is similarly hypertrophied in hypertension and aortic stenosis. If the work of the heart is much increased, the left portion of the deep sinospiral may also hypertrophy.

5. The surface portions of the two superficial muscles do not have a measurable variation in thickness. When intraventricular pressure is increased, the papillary portion of these superficial muscles hypertrophies. Conversely, in a heart with a "buttonhole" mitral opening and calcified leaves, the papillary muscles were atrophied.

6. If the surface muscles are variable in distribution, or if they are deficient, apparent discrepancies might occur when localizing points of initial negativity, the origin of premature beats, etc.

7. For surface localization of electrical phenomena, accurate sketches of the surface distribution of the cleaned muscle should be provided.

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THE EFFECT OF DIGITALIS ON THE FORM OF THE HUMAN ELECTROCARDIOGRAM, WITH SPECIAL REFERENCE TO CHANGES OCCURRING IN THE CHEST LEAD*

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IN 1913 Cohn and Fraser¹ observed inversion of the T-waves of the human electrocardiogram following the administration of digitalis. In a more detailed study two years later these authors together with Jamieson² described changes in the form of the T-waves and R-T segments of the three standard leads following the use of this drug. Since then other papers^{3, 4, 5} relating to this subject have appeared.

Recently it has been shown that electrocardiograms derived from precordial leads may reveal early and characteristic changes in the presence of myocardial infarction.⁶ We have found that digitalis also alters the form of the precordial electrocardiogram and that these changes may be confused with those resulting from coronary artery disease. There have appeared in the literature only a few brief references^{7, 8, 9, 10} to these changes and only one short paper¹¹ devoted to them. In this report we shall describe the alterations which we have observed in the chest lead of the electrocardiogram following the administration of therapeutic amounts of digitalis.

PLAN OF OBSERVATION

There are thirty patients in whom the three standard leads as well as a chest lead were taken, not only before but also after the administration of therapeutic amounts of digitalis. All but five of them were in a basal metabolic state (Tables I and II) when the records were taken. With one exception (Case 30), the patients suffered from organic lesions of the cardiovascular system. The etiologic diagnosis was rheumatic fever in 17 patients, rheumatic fever and hypertension in 1,[†] hypertension in 4, hypertension secondary to chronic glomerular nephritis in 1,[‡] arteriosclerosis in 4, and syphilis in 2. The examination of one patient who suffered from attacks of paroxysmal auricular flutter failed to reveal evidence of organic heart disease. Twenty-one patients exhibited no signs of congestive heart failure at the time these observations were made; the remaining nine were decompensated. Normal sinus rhythm was present in 27, and auricular fibrillation in the remaining 3 (Tables I and II). One patient (Case 19) exhibited intraventricular heart block (left bundle branch type, new terminology).

The preparation of dried digitalis leaves made and distributed by the American Heart Association[§] was used. All patients received digitalis prepared from the

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†Included under the Rheumatic Group in Table I.

‡Included in the Hypertensive Group in Table II.

§0.1 gm. equivalent to one cat unit.

same batch. We found by experience that 1.8 gm. of this batch given within a period of twenty-four hours is an effective digitalizing amount.* It was the plan to give the digitalizing amount rapidly so that it might be absorbed within twenty-four hours after the initial dose. To this end 22 patients received 1.8 gm. of digitalis within a period of twenty hours. Of the eight other patients one† (Case 4) received 1.6 gm. within a period of eight hours; two (Cases 5 and 24), 1.7 gm. within twelve hours; one (Case 17), 1.9 gm. within thirteen hours; two (Cases 12 and 22), 1.8 gm. within twenty-three hours; one (Case 23), 2.0 gm. within twenty-eight hours; and one patient (Case 30) received 2.2 gm. within thirty hours. With but slight variation the method of digitalization was as follows: After a control record had been obtained, the patient was given 0.8 gm. of digitalis as the initial dose; this was followed four hours later by 0.5 gm. and then by 0.3 gm. and 0.2 gm. at four-hour intervals, making a total of 1.8 gm.

The chest lead was derived by placing the right arm electrode just within the apex and the left arm electrode in the left interscapular region. At the time the control record was taken, a mark was left on the chest wall at the site of the anterior electrode so that later records could be secured from the same area. This precordial derivation of the electrocardiogram in most normal adults is characterized by negative P-waves and T-waves and rather large diphasic Q-R complexes. The R-T segment is commonly depressed 1 to 2 mm. below the isoelectric line, and the T-wave varies between 6 and 10 mm. in depth. In making our observations, the standardization was such that one millivolt deflected the string 1 cm.; correction was not made for small errors in standardization. The time interval between the initial dose of digitalis and the first electrocardiogram after digitalization had been completed did not exceed thirty hours in 26 of the 30 cases (Tables I and II). Usually two or more records were taken after digitalization had been completed, and all but five patients received maintenance amounts of digitalis during the period of study.

OBSERVATIONS

Changes in the Three Standard Leads.—In every case changes in the form of the T-waves and R-T segments occurred in one or more of the three standard leads after therapeutic amounts of digitalis had been given. The cases‡ may be divided into three groups according to the changes which took place in the form of the T-waves. In the first group there are 18 patients (Cases 1, 2, 4, 6, 7, 9, 15, 16, 17, 18, 19, 21, 22, 24, 26, 28, 29 and 30). In these cases the T-wave decreased in its positive phase or increased in its negative phase in all three leads. In the second group, comprised of seven patients (Cases 3, 13, 14, 20, 23, 25, and 27), the T-wave increased in its positive phase in Lead I and decreased in its positive phase or increased in its negative phase in Lead III. The five patients remaining fall in a third group (Cases 5, 8, 10, 11, and 12). In these the T-wave remained unchanged in one of the leads and decreased in its positive phase or increased in its negative phase in the other two leads.

*Experience with this particular batch showed that, regardless of body weight, it was necessary to give this amount within twenty-four hours to slow the rapid ventricular rate in the presence of auricular fibrillation to about 70 per minute; it was considered the digitalizing amount.¹²

†Patient complained of slight nausea after 1.6 gm. were given.

‡In one of the patients (Case 23) the third lead was not obtained in the first record taken after digitalization had been completed; the next record, taken two days later, was used for comparison with the control (Table II).

TABLE I

THE EFFECT OF DIGITALIS ON THE FOUR-LEAD ELECTROCARDIOGRAM OF SUBJECTS SUFFERING FROM RHEUMATIC HEART DISEASE WITH AND WITHOUT CONGESTIVE HEART FAILURE

CASE AND HOSPITAL NUMBER	AGE (YR.)	"DIAGNOSIS	DATE	AMOUNT OF DIGITALIS GIVEN (GAL.)	A-V CONDUCTION TIME (SEC.)	RATE PER MIN.	AXIS DEVIATION	SUMMARY OF CHANGES IN QUESST LEAD AFTER DIGITALIZING AMOUNT ONLY		TIME WITH REFERENCE TO INITIAL DOSE OF DIGITALIS
								R-T SEGMENT	T-WAVE	
<i>Rheumatic Heart Disease Without Failure</i>										
11 J. S. 61475 ♀	28	M.S., and M.I., E.H. N.S.R. Class I or IIa Pregnancy 7 mo.	10/ 8/34	1.8	0.17	107	right	Not changed	Negative to diaphasic	Before 25 hr. after
			10/10/34	0.34	0.18	80	right			
			10/11/34	0.2	0.18	94	right			
			10/18/34	(daily)	0.19	97	right			
21 R. D. 68341 ♀	28	M.S., and M.I., E.H. N.S.R. Class IIa Pregnancy 5-6 mo.	10/20/34	1.8	0.18	94	none	Depressed to isoelectric	Negative to less negative	Before 25 hr. after
			10/22/34	0.2	0.19	84	none			
			10/30/34	(daily)	0.18	88	none			
31 E. P. 14505 ♂	21	M.S., M.I., A.S. and A.I., E.H. N.S.R. Class IIa	11/ 8/34	1.8	0.20	65	left	Not changed	Negative to less negative	Before 26 hr. after
			11/10/34	0.2	0.20	61	left			
			11/13/34	(daily)	0.22	60	left			
			11/15/34		0.20	60	left			
41 A. G. 79037 ♂	23	M.S. and M.I., E.H. N.S.R. Class I	11/12/34	1.6	0.20	70	none	Not changed	Negative to less negative	Before 27 hr. after
			11/14/34		0.20	65	none			
			11/17/34		0.22	59	none			
			1/10/35		0.22	70	none			

*In this table as well as in Table II, the following abbreviations are used:

The diagnoses in this paper conform to the nomenclature for cardiac diagnosis recommended by the Heart Committee of the New York Tuberculosis and Health Association. "Criteria for the Classification and Diagnosis of Heart Diseases," ed. 2, New York Tuberculosis and Health Association, New York, 1929.

M.S. = Mitral stenosis; M.I. = mitral insufficiency; E.H. = enlarged heart; N.S.R. = normal sinus rhythm; A.S. = aortic stenosis; A.I. = aortic insufficiency; A.P. = auricular fibrillation.

†Indicates patient was in a basal metabolic state at the time records were obtained.

‡In this case as well as in the subsequent cases maintenance amounts of digitalis were not given until after the first record following digitalization had been obtained.

TABLE I—CONT'D

5† A. M. 37709 ♀	23	M.S., M.I. and A.I., E.H. N.S.R. Class I or IIa	2/14/35 2/16/35	1.7	0.18 0.18	72 60	left left	Not changed	Negative to less negative	Before 27 hr. after
6† E. C. 33078 ♀	19	M.S., M.I., A.I. and A.S., E.H. N.S.R. Class I	3/18/35 3/20/35 3/21/35	1.8	0.18 0.18 0.19	71 68 67	none none none	Not changed	Negative to less negative	Before 27 hr. after
7† R. L. 90113 ♂	20	M.S., M.I. and A.I., E.H. N.S.R. Class IIa	4/ 6/35 4/ 8/35 4/ 9/35	1.8 0.3	0.14 0.15 0.15	61 75 62	none none none	Not changed	Negative to less negative	Before 29 hr. after
8† F. S. 89187 ♂	24	M.S. and M.I., E.H. N.S.R. Class I	4/13/35 4/15/35 4/16/35 4/19/35	1.8	0.18 0.22 0.23 0.21	75 52 65 70	right right right right	Not changed	Diphasic to less negative	Before 28 hr. after
9† J. F. 31027 ♀	26	M.S., M.I., A.S. and A.I., E.H. N.S.R. Class I	5/18/35 5/20/35 5/21/35 5/22/35	1.8 0.2	0.16 0.16 0.16	70 52 70	none none none	Isoelectric to elevated	Negative to diphasic	Before 28 hr. after
10 H. K. 96957 ♀	36	M.S., M.I. and A.I., E.H. N.S.R. Class IIa	6/15/35 6/16/35 6/17/35	1.8	0.23 0.26 0.24 to 0.26	88 86 88	left left left	Not changed	Form changed slightly	Before 24 hr. after
11 L. D. 98021 ♀	37	M.S., M.I., A.S. and A.I., E.H. N.S.R. Class IIa Pregnancy 6 mo.	9/18/35 9/19/35 9/20/35	1.8 0.1	0.16 0.22 0.22	125 83 91	right right right	Isoelectric to elevated	Diphasic to positive	Before 23 hr. after
12 P. K. 100918 ♀	41	No valvular disease Class F Pregnancy 9 mo.	9/17/35 9/18/35 9/19/35 9/20/35	1.8 0.1 0.1	0.14 0.16 0.15 0.15	100 94 100 91	left left left left	Not changed	Negative to less negative	Before 28 hr. after

TABLE I—Continued

CASE AND HOSPITAL NUMBER	AGE (YR.)	*DIAGNOSIS	DATE	AMOUNT OF DIGITALIS GIVEN (GM.)	A-V CONDUCTION TIME (SEC.)	RATE PER MIN.	AXIS DEVI- ATION	SUMMARY OF CHANGES IN CHEST LEAD AFTER DIGITALIZ- ING AMOUNT ONLY		TIME WITH REFERENCE TO INITIAL DOSE OF DIGITALIS
								R-T SEGMENT	T-WAVE	
131 C. W. 88345 ♂	25	M.S. and M.L., E.H. N.S.R. Class I	12/19/35	1.8	0.22	60	right	Not changed	Positive to diphasic and decreased positive phase	Before 27 hr. after
			12/21/35	0.2 (daily)	0.21	42	right			
			12/23/35		0.22	60	right			
144 W. M. 126827 ♂	47	A.S. and A.L., E.H. N.S.R. Class IIa	3/30/36	1.8	0.16	71	none	Not changed	Diphasic to increased negative and positive phases and changed form	Before 26 hr. after
			4/ 1/36	0.2	0.17	88	none			
			4/ 2/36		0.16	73	none			
145 B. S. 147113 ♂	17	M.S., M.L., A.S. and A.L., E.H. N.S.R. Class IIa	11/27/36	1.8	0.20	88	none	Not changed	Negative to less negative	Before 26 hr. after
			11/28/36	0.1 (daily)	0.20	81	none			
			11/30/36		0.19	83	none			
Rheumatic Heart Disease With Failure										
164 M. C. 119155 ♀	53	M.S. and M.L., E.H. Hypertension A.F. Class IIb	1/28/36	1.8	A.F.	126	none	Not changed	Negative to less negative	Before 28 hr. after
			1/30/36	0.2 (daily)	A.F.	80	none			
			2/ 1/36		A.F.	90	none			
171 S. S. 123829 ♂	32	M.S., M.L. and A.L., E.H. N.S.R. Class IIb	2/19/36	1.9	0.26	75	right	Not changed	Negative to less negative	Before 27 hr. after
			2/21/36	0.2 (daily)	0.30	56	right			
			2/24/36		0.32	52	right			
181 G. Mac P. 121205 ♂	57	M.S. and M.L., E.H. A.F. Class IIb	2/25/36	1.8	A.F.	108	none	Isoelectric to elevated	Positive to increased amplitude	Before 29 hr. after
			2/27/36	0.2 (daily)	A.F.	80	none			
			2/29/36		A.F.	70	none			

In every case except two, the R-T segments became isoelectric, depressed, or more depressed in one or more of the three standard leads following digitalization. That is to say, there was a general tendency toward depression of the R-T segment in these cases. In the two exceptions mentioned above (Cases 3 and 20), however, isoelectric R-T segments in the third lead became elevated after digitalis. In those patients receiving maintenance amounts of digitalis, later records showed usually that the changes as already described in the T-waves and R-T segments became more marked; in a few instances, however, the T-waves varied only slightly (Tables I and II).

Changes in the Chest Lead.—Changes in the form of the chest lead were evident in the first record taken after digitalization in 29 of the 30 patients. These 29 patients fall into ten groups according to the changes which were observed in the form of the T-waves.

1. The case of A. G. (Case 4) serves to illustrate the change that occurred in 15 instances (Cases 2, 3, 4, 5, 6, 7, 12, 15, 16, 17, 21, 25, 26, 27 and 28) in which a negative T-wave became less negative (Fig. 1).

2. The case of J. F. (Case 9) serves to illustrate the change that occurred in three instances (Cases 1, 9 and 30) in which a negative T-wave became diphasic (Fig. 2).

3. The case of C. M. (Case 22) illustrates the change that occurred in one instance in which a negative T-wave became positive (Fig. 3).

4. The case of L. B. (Case 20) serves to illustrate the change that occurred in three instances (Cases 8, 20 and 23) in which a diphasic T-wave decreased in its negative phase, and, in one of these, increased in its positive phase also (Fig. 4).

5. The case of C. McA. (Case 24) illustrates the change that occurred in one instance in which a diphasic T-wave increased in its positive phase only (Fig. 5).

6. The case of L. D. (Case 11) illustrates the change that occurred in one instance in which a diphasic T-wave became positive (Fig. 6).

7. The case of G. MacF. (Case 18) illustrates the change that occurred in one instance in which a positive T-wave increased in amplitude (Fig. 7).

8. The case of C. W. (Case 13) serves to illustrate the change that occurred in two instances (Cases 13 and 29). In one of these (Case 13) a positive T-wave became diphasic and decreased in its positive phase (Fig. 8); in the other (Case 29) a diphasic T-wave became negative and increased in its negative phase.

9. In one instance (Case 14) a diphasic T-wave increased in both its positive and negative phases.

10. In one instance (Case 10) no change occurred in the amplitude of the T-wave, but its contour was altered.

In short, after the administration of therapeutic amounts of digitalis the T-wave in twenty-five cases (those cases included in the first seven

TABLE 11

THE EFFECT OF DIGITALIS ON THE FOUR-LEAD ELECTROCARDIOGRAM OF PATIENTS SUFFERING FROM HYPERTENSIVE, ARTERIOSCLEROTIC AND SYSTOLIC HEART DISEASE WITH AND WITHOUT CONGESTIVE HEART FAILURE, AS WELL AS OF ONE NORMAL INDIVIDUAL

CASE AND HOSPITAL NUMBER	AGE (YR.)	DIAGNOSIS	DATE	AMOUNT OF DIGITALIS GIVEN (GM.)	A-V CONDUCTION TIME (SEC.)	RATE (PER MIN.)	AXIS DEVIATION	SUMMARY OF CHANGES IN Q-TEST LEAD AFTER DIGITALIZING AMOUNT ONLY		TIME WITH REFERENCE TO INITIAL DOSE OF DIGITALIS
								R-T SEGMENT	T-WAVE	
Hypertensive Heart Disease Without Failure										
19* A. G. 123489 ♀	62	Arteriosclerosis H.L.—V. H-B. N.S.R. Class I	3/11/36 3/13/36 3/14/36	1.8 0.2	0.16 0.18 0.18	77 71 65	left left left	Not changed	Not significantly changed	Before 26 hr. after
Hypertensive Heart Disease With Failure										
20* L. B. 124739 ♂	64	Arteriosclerosis, E.H. N.S.R. Class IIb	2/29/36 3/ 2/36 3/ 6/36	2.0 0.2 (daily)	0.16 0.18 0.18	100 64 70	left left left	Not changed	Diphasic to decreased negative phase	Before 46 hr. after
21* E. B. 94711 ♂	41	Arteriosclerosis, E.H. N.S.R. Class IIb	5/11/35 5/13/35	1.8	0.15 0.16	100 83	none none	Not changed	Negative to less negative and changed form	Before 29 hr. after
22 C. M. 113159 ♂	34	Chronic Glomerular Nephritis Secondary Hypertension, E.H. N.S.R. Class III	11/11/35 11/13/35	1.8	0.15 0.16	103 83	left left	Depressed to isoelectric	Negative to positive	Before 41 hr. after
23* A. F. 118112 ♂	38	E.H. N.S.R. Class III	1/ 4/36 1/ 6/36 1/ 8/36 1/15/36	2.0 0.2 (daily)	0.16 0.16 0.17 0.18	94 73 75 65	left left left left	Depressed to less depressed	Diphasic to decreased negative phase and increased positive phase	Before 46 hr. after

*Indicates patient was in basal metabolic state when records were obtained.

†L.L.—V. H-R. = Intraventricular heart block (left bundle branch type (new terminology)).

TABLE II—CONT'D

Arteriosclerotic Heart Disease Without Failure										
24*	C. McA. 14258 ♂	68	Coronary Artery Disease, M.I. N.S.R. Class IIa	1/15/35 1/17/35 1/19/35	1.7 0.15 0.16	70 75 70	none none none	Isoelectric to elevated	Diphasic to re- versed order of phases and increased positive phase	Before 26 hr. after
25*	J. S. 109757 ♂	58	Coronary Artery Disease N.S.R. Class IIa	10/29/35 10/31/35 11/ 4/35 11/ 6/35	1.8 0.1-0.2 (daily) 0.18 0.18 0.18	57 52 61 60	left left left left	Depressed to isoelectric	Negative to less negative	Before 26 hr. after
26*	M. M. 123080 ♀	57	Coronary Artery Disease, E.H. A.F. Class IIa	2/15/36 2/17/36 2/21/36	1.8 0.2-0.3 (daily) A.F. A.F. A.F.	136 95 90	none none none	Isoelectric to elevated	Negative to less negative	Before 25 hr. after
Arteriosclerotic Heart Disease With Failure										
27*	C. K. 99561 ♂	48	Coronary Thrombosis N.S.R. Class IIb	11/13/35 11/15/35 11/18/35	1.8 0.2 (daily) 0.16 0.20 0.18	111 105 103	none none none	Not changed	Negative to less negative and changed form	Before 26 hr. after
Syphilitic Heart Disease Without Failure										
28*	H. W. 71762 ♂	48	Syphilitic Aortitis A.I., E.H. N.S.R. Class I	10/17/34 10/19/34 10/23/34 10/26/34	1.8 0.2 (daily) 0.18 0.18 0.18	63 61 61 59	none none none none	Depressed to isoelectric	Negative to less negative 	Before 26 hr. after
Syphilitic Heart Disease With Failure										
29*	J. K. 129406 ♂	55	Syphilitic Aortitis A.I., E.H. N.S.R. Class III	4/15/36 4/17/36 4/20/36	1.8 0.18 0.20-0.21 0.18	88 120 97	none none left	Depressed to more de- pressed	Diphasic to negative with increased neg- ative phase and changed form also	Before 27 hr. after
Normal Heart										
30*	H. B. 113637 ♂	21	No evidence of heart disease N.S.R.	12/18/35 11/26/35 11/27/35 11/29/35	1.0 1.2 0.15 0.15	65 91	none none	Not changed	Negative to diphasic	3 wk. after stopping digitalis 66 hr. after

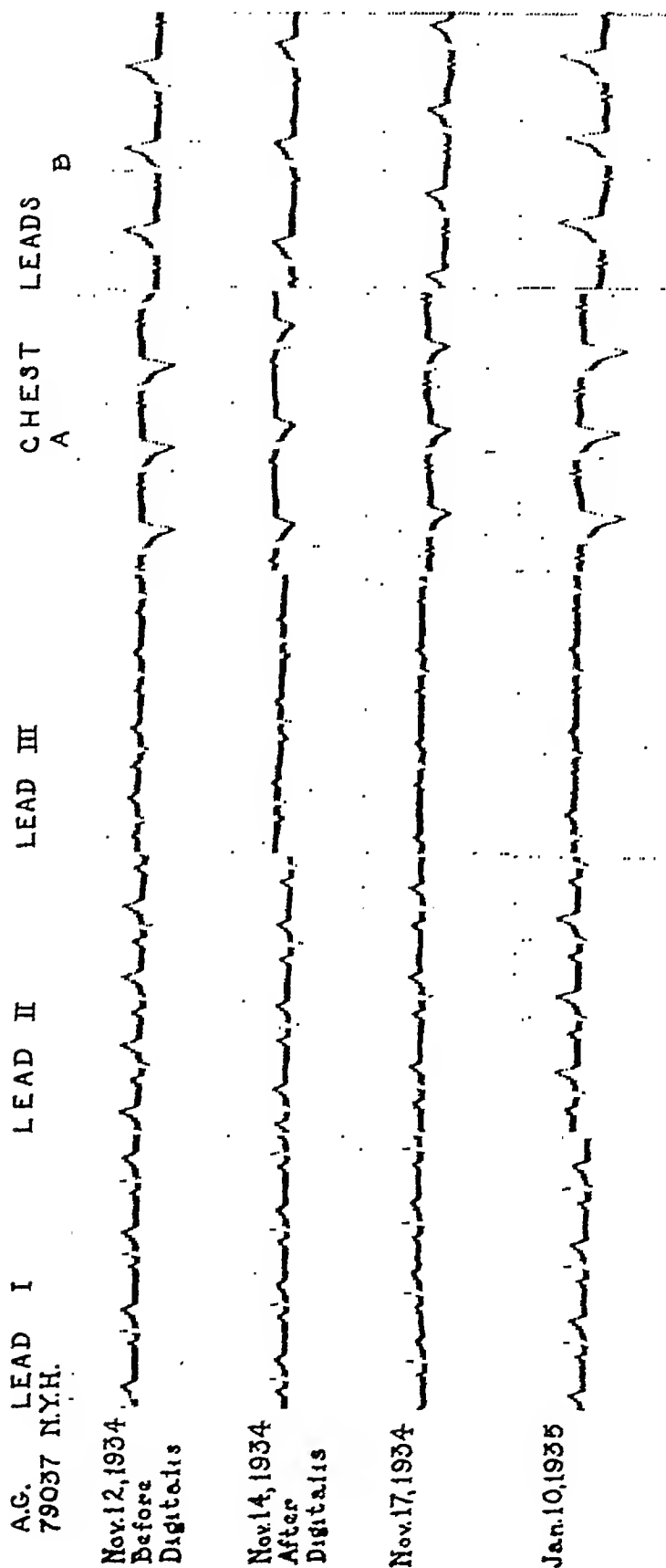


Fig. 1.—In this figure as well as in Figs. 2 to 8, inclusive, reproductions of the three standard leads and two chest leads are shown. Chest lead A is a reproduction of the original tracing (see text). In chest lead B the original film is printed so that the tracing is like that which would be derived by reversing the order of the electrodes on the chest, that is to say, from placing the left arm electrode anteriorly and the right arm electrode posteriorly. This was done so that the second chest lead would be comparable to the derivation to be recommended by the American Heart Association's Committee on Standardization of the Chest Lead.¹³ The first tracing in each figure is the control record. The standardization in all records was such that 1 millivolt produced a 1 centimeter deflection of the string. Divisions of the ordinates equal 10.4 volt. Divisions of the abscissae equal 0.01 sec. The electrocardiograms in all figures are reduced to five-elevenths of their natural size. In this figure the electrocardiograms of A. G. (Case 4) are reproduced. The records in this case serve to illustrate the change that occurred in fifteen instances in which negative T-waves in the chest lead became less negative after digitalis. This patient received 1.6 gm. of digitalis between 6:00 A.M. and 6:00 P.M. on Nov. 13, 1934. In this case maintenance amounts of digitalis were not given, and the T-waves in the chest lead as well as in the three standard leads returned toward their original form.

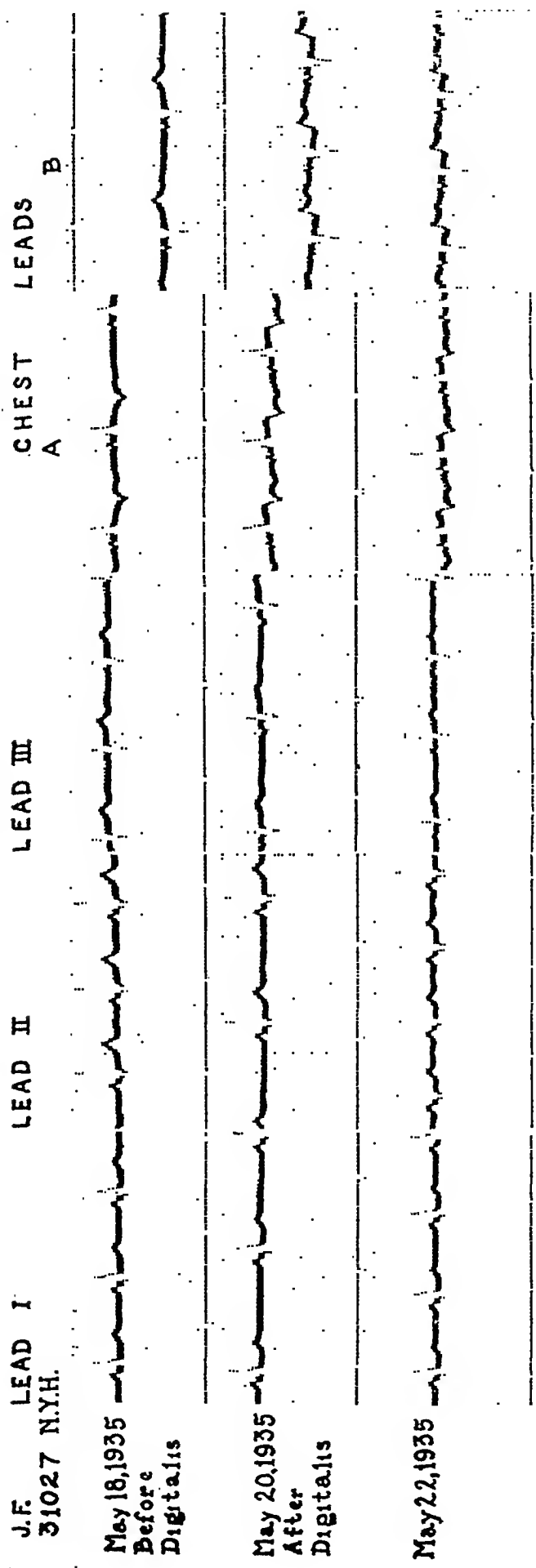


Fig. 2.—In this figure the electrocardiograms of J. F. (Case 9) are reproduced. The records in this case serve to illustrate the change that occurred in three instances in which negative T-waves in the chest lead became diphasic after the administration of digitalis. This patient received 1.8 gm. of digitalis between 6:00 A.M. and 6:00 P.M. on May 19, 1935, and 0.2 gm. additional on May 21, 1935.

groups above) became less negative, diphasic, or positive; if diphasic beforehand, it decreased in its negative phase or increased in its positive phase or exhibited both changes; if already positive, it increased in amplitude only. In two cases (included in Group 8) the reverse

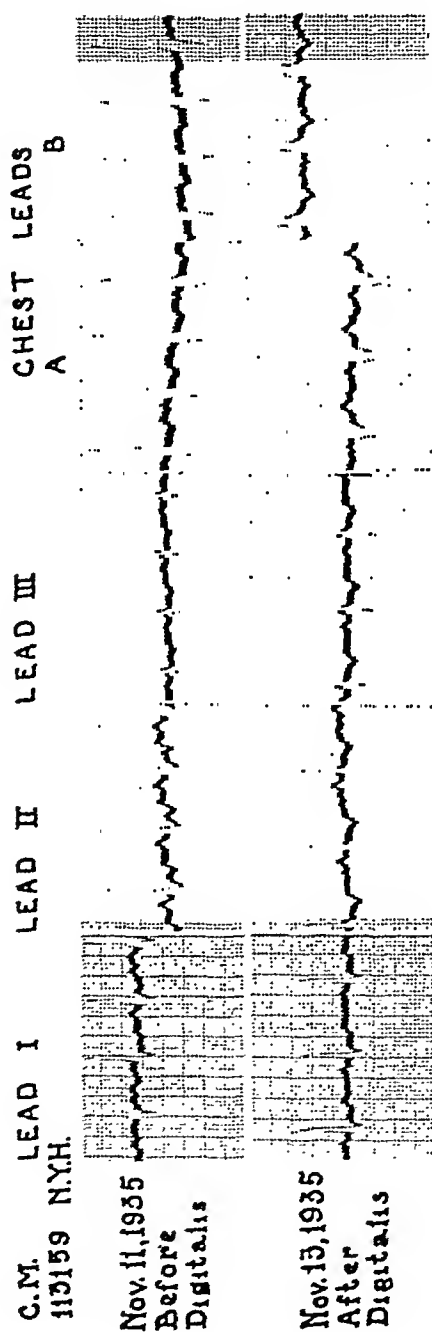


Fig. 3.—In this figure the electrocardiograms of C. M. (Case 22) are reproduced. The records in this case illustrate the change that occurred in one instance in which negative T-waves in the chest lead became positive after the administration of digitalis. This patient received 1.5 gm. of digitalis between 6:00 p.m. on Nov. 11, 1935, and 4:00 p.m. on Nov. 12, 1935.

change occurred, the T-wave decreasing in its positive phase and increasing in its negative phase. In the remaining two cases (Groups 9 and 10) the alterations were different still. In one (Case 10) of these, however, a negative T-wave became diphasic in a later record (Table I) thus placing it in the second group above.

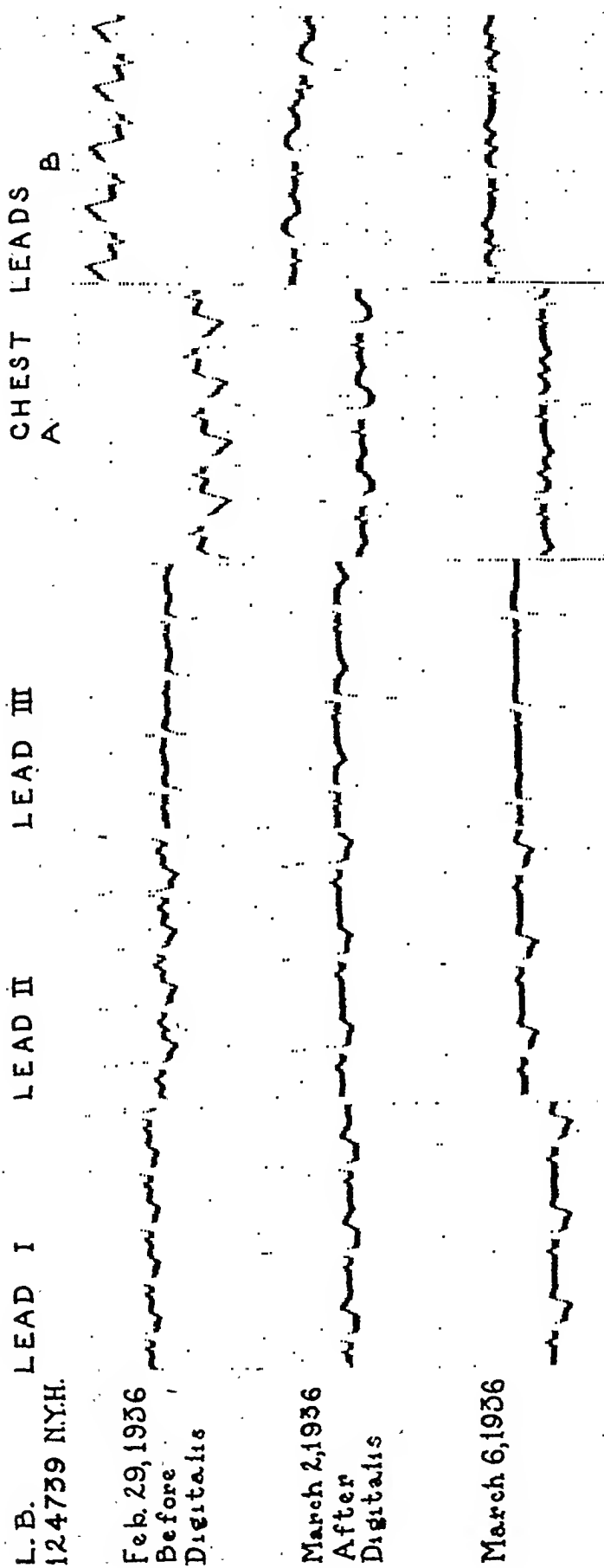


Fig. 4.—In this figure the electrocardiograms of L. B. (Case 20) are reproduced. The records in this case serve to illustrate the change that occurred in three instances in which alphasic T-waves in the chest lead decreased in their negative phase after the administration of digitalis. This patient received 2.0 gm. of digitalis between 12:00 M. on Feb. 29, 1936, and 4:00 P.M. on March 1, 1936. During the remainder of the period of study he received 0.2 gm. daily as a maintenance dose.

In one patient only (Case 19) did the form of the chest lead remain unchanged after digitalization. Twenty-four hours later, this patient

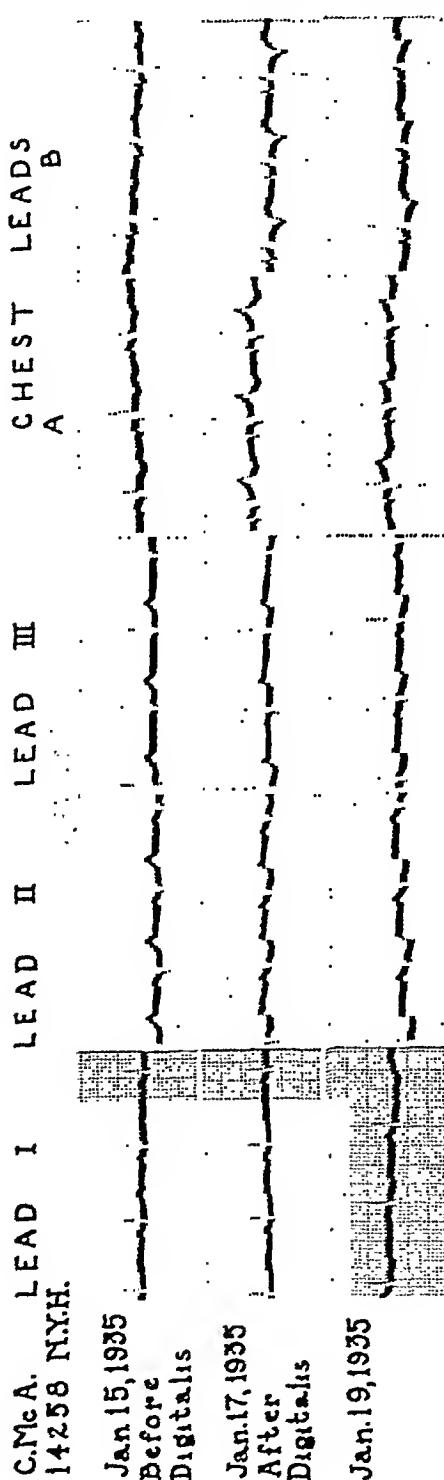


Fig. 5.—In this figure the electrocardiograms of C. McA. (Case 24) are reproduced. The records in this case illustrate the change that occurred in one instance in which diphasic T-waves in the chest lead increased in their positive phase only after the administration of digitalis. This patient received 1.7 gm. of digitalis between 9:00 A.M. and 9:00 P.M. on Jan. 16, 1935. Maintenance amounts of digitalis were not given to this patient.

having received 0.2 gm. of digitalis, the form of the T-waves and R-T segments was still unaltered. In this case the T-wave was positive, and the R-T segment isoelectric.

The changes in the R-T segments in the chest lead were not as marked as those in the T-waves. In nineteen cases no significant change was observed in this part of the electrocardiogram in the first record taken after digitalization had been completed. In ten patients (Cases 2, 9, 11, 18, 22, 23, 24, 25, 26 and 28) the R-T segment became

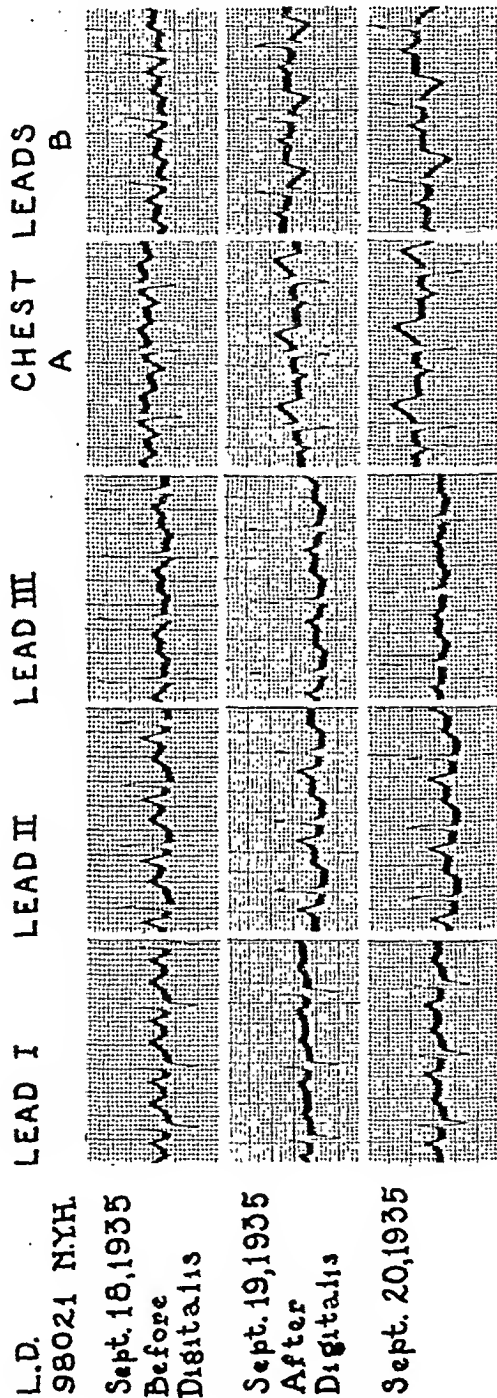


Fig. 6.—In this figure the electrocardiograms of L. D. (Case 11) are reproduced. The records in this case illustrate the change that occurred in one instance in which diphasic T-waves in the chest lead became positive after the administration of digitalis. This patient received 1.8 gm. of digitalis between 1:00 p.m. on Sept. 18, 1935, and 7:00 a.m. on Sept. 19, 1935, and 0.1 gm. additional on Sept. 20, 1935.

less depressed, isoelectric, or elevated; in short, there was a tendency toward elevation of the R-T segment in these cases. In one instance only (Case 29) did the R-T segment become more depressed after digitalis. In this case the T-wave which was diphasic before digitalis became negative and increased in its negative phase.

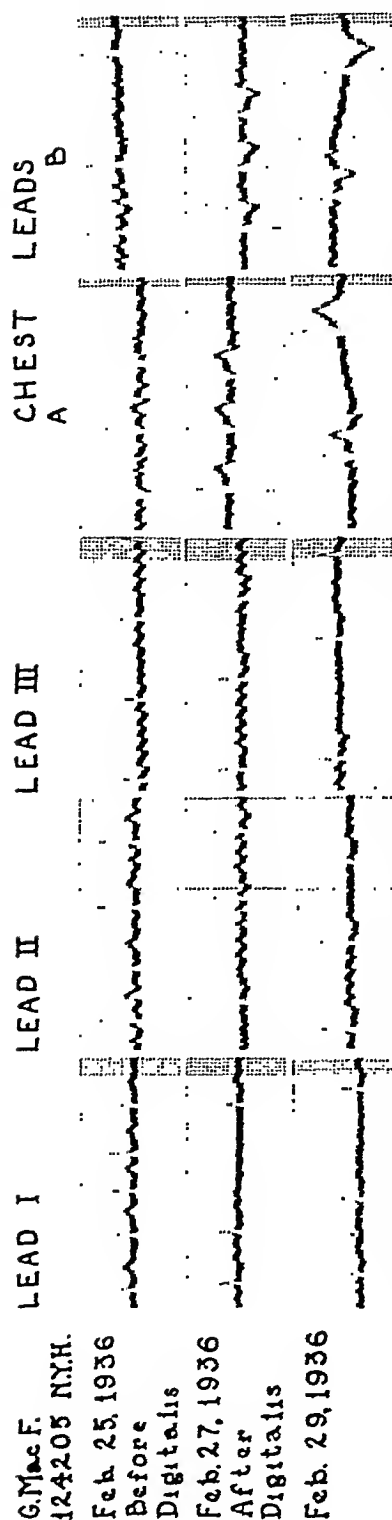


Fig. 7.—In this figure the electrocardiograms of G. MacF. (Case 18) are reproduced. The records in this case illustrate the change that occurred in one instance in which positive T-waves in the chest lead increased in amplitude after the administration of digitalis. This patient received 1.8 gm. of digitalis between 8:00 A.M. and 9:00 P.M. on Feb. 26, 1936. He was then kept on a maintenance dose of 0.2 gm. daily for the remainder of the period of study.

When maintenance amounts of digitalis were given the alterations in the form of the chest lead usually became more marked. On the other hand, the T-wave returned toward its predigitalization configuration in the five instances (Cases 4, 6, 8, 24, and 29) in which maintenance amounts of the drug were not given (Tables I and II).

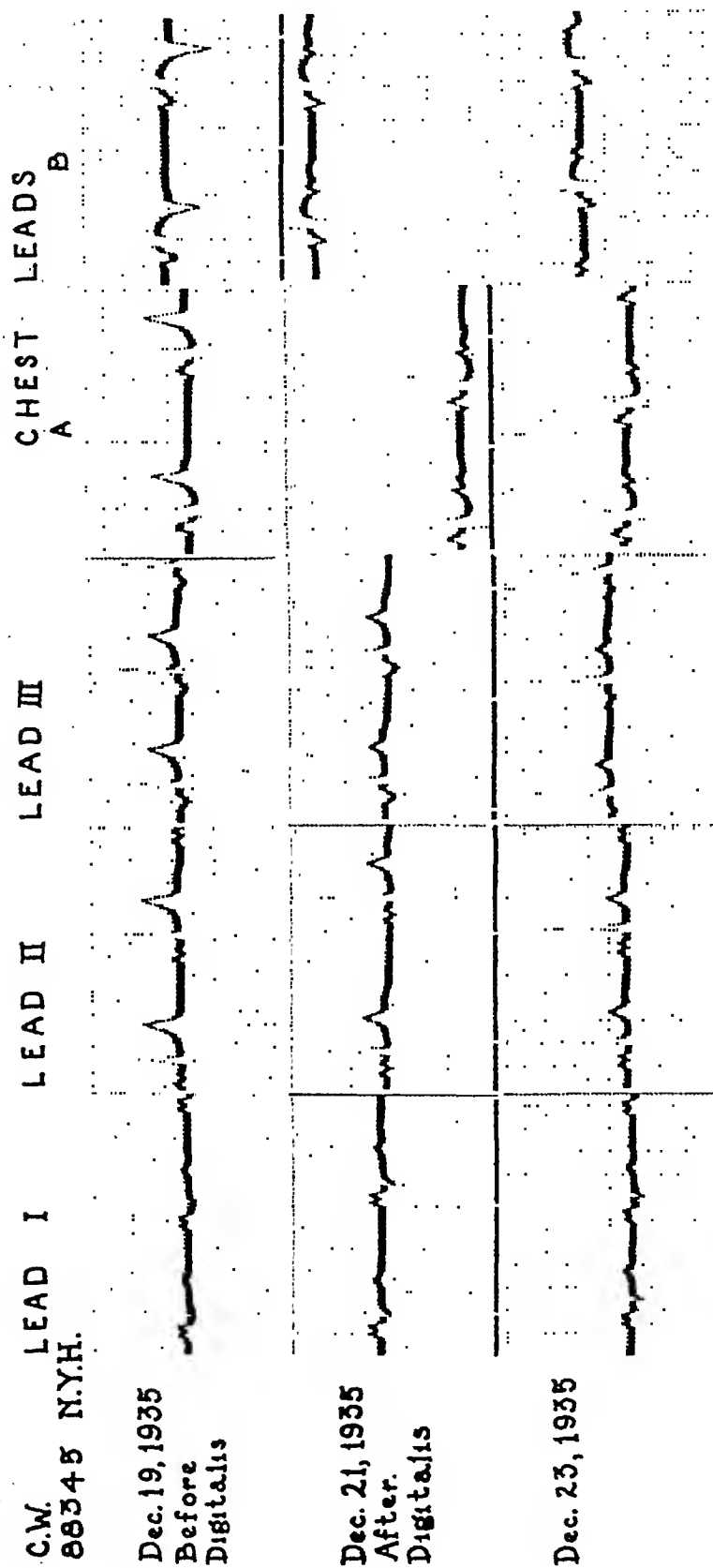


Fig. 8.—In this figure the electrocardiograms of C. W. (Case 13) are reproduced. The records in this case serve to illustrate the change that occurred in two instances. In this case positive T-waves in the chest lead became diphasic and decreased in their positive phase after the administration of digitalis. This patient received 1.8 gm. of digitalis between 8:00 A.M. and 8:00 P.M. on Dec. 20, 1935. He then received 0.2 gm. daily as a maintenance dose during the remainder of the period of study.

The changes induced by digitalis in the form of the T-waves and R-T segments in the chest lead bear close enough resemblance to those resulting from myocardial infarction and coronary artery disease to lead to confusion. In the interpretation of the chest lead effort should be made, therefore, to ascertain whether digitalis has been given.

SUMMARY

1. The administration of therapeutic amounts of digitalis induces changes in the form of the T-waves and R-T segments of the chest lead as well as the three standard leads of the human electrocardiogram.

2. In most instances after exhibition of the digitalis effect, the T-wave in the chest lead became less negative, diphasic, or positive; if already diphasic, it became less negative or increased in its positive phase or exhibited both changes; if already positive, it increased in amplitude only. The R-T segments often became less depressed, isoelectric, or elevated. However, the reverse of these changes in the T-waves and R-T segments may occur occasionally.

3. Changes in the chest lead were induced by digitalis irrespective either of the etiologic type of heart disease or of the state of cardiac compensation, a fact which has already been established for the three standard leads.^{2, 4}

4. The changes induced by digitalis in the form of the T-waves and R-T segments of the chest lead may resemble those resulting from coronary artery disease or recent coronary occlusion and lead to confusion in the interpretation of the record if it is not known that the drug has been given.

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Department of Clinical Reports

AN ATTEMPT TO OBLITERATE THE PATENT DUCTUS ARTERIOSUS IN A PATIENT WITH SUBACUTE BACTERIAL ENDARTERITIS*

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OF ALL the complications of heart disease none is of more interest than *Streptococcus viridans* infection, and this equally whether one considers the nature of the invading organism, the structural changes in the heart necessary for its gaining a foothold, or the hopelessness of treatment. Although this complication is most commonly seen in relation to chronic rheumatic heart disease, its relative incidence is far greater in certain types of congenital heart disease. Thus in Abbott's series¹ of 92 cases of simple patency of the ductus arteriosus, death was caused by bacterial endarteritis or endocarditis in no less than 21. Recovery from this complication is extremely rare² as there is no specific medical treatment. For this reason heroic measures are often justified. The following report is an account of what we believe is the first attempt on record to obliterate the patent ductus arteriosus in a patient with *Streptococcus viridans* infection.

CASE REPORT

C. McK., a pleasant tempered young woman, twenty-two years of age, entered the Evans Memorial Hospital on Feb. 19, 1937, complaining of weakness and nausea. Although frail when a child, she had never suffered from any serious illness. At the time she began school, her parents were told by the school physician that she had a heart murmur. However, except for becoming short of breath a little more readily than her companions, she never had had symptoms related to her heart. Three months before hospital entry she began to complain of easy fatigability and malaise. Shortly thereafter she was found to have a temperature of 100° F. and was advised to go to bed. She soon developed intractable nausea and vomiting and, some time later, attacks of sharp pain in the chest which were aggravated by deep breathing and coughing. She gradually lost weight and strength and, shortly before admission, began to raise blood-streaked sputum.

Physical examination revealed a rather poorly developed, undernourished individual. The skin was pale, warm, and dry. No petechiae were found. The heart was not enlarged although the outer border of percussion dullness in the second and third left interspaces exceeded the normal. The heart rate was 104 a minute, and the rhythm was regular. In the second interspace to the left of the sternum there was heard a loud, continuous murmur with systolic accentuation. In the same area

*From the Evans Memorial and the Thoracic Surgery Service of the Massachusetts Memorial Hospitals.

there could be felt a thrill accompanying the systolic phase of the murmur. At the several valve areas no murmur was heard save the systolic phase of the continuous murmur which was widely transmitted. The pulmonary second sound was accentuated and was much louder than the aortic second sound. The blood pressure was 90 mm. Hg systolic and 60 mm. diastolic. The venous pressure was normal. The lungs were clear and resonant. The abdomen was soft. The liver and the spleen were not palpable. There was no clubbing of the fingers or the toes.

Teleroentgenograms of the chest showed several areas of soft infiltration throughout both lung fields; the heart was not enlarged, but there was moderate dilatation and increased pulsation in the region of the pulmonary artery. The electrocardiogram was normal save for slight inversion of the T-waves in Leads II and III. Blood studies revealed a slight leucocytosis and a moderate achromic anemia. Repeated blood cultures were positive for the *Streptococcus viridans*. Examination of the urine revealed a very slight trace of albumin and rare granular casts but no red blood cells.

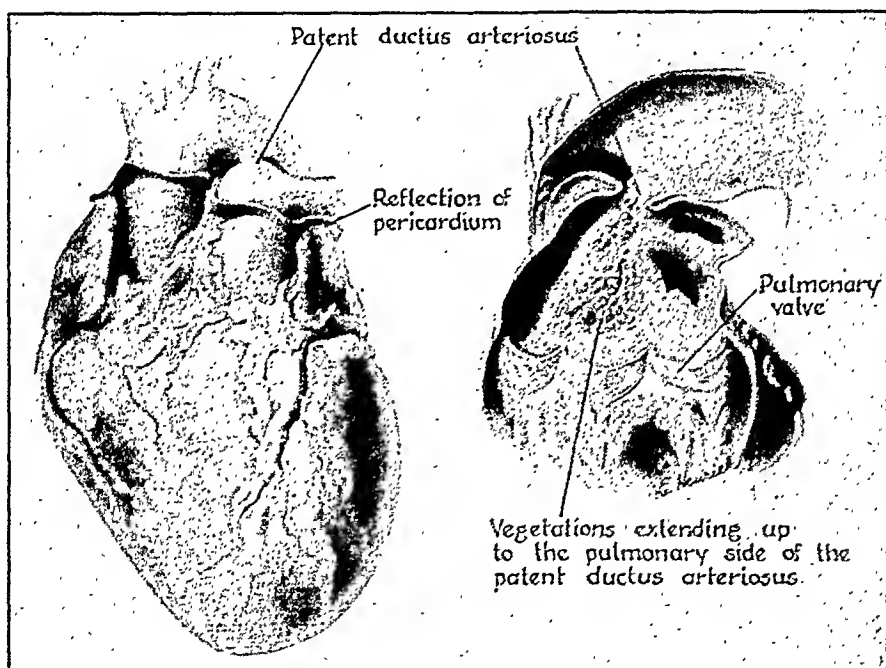


Fig. 1.

A diagnosis was made of congenital patency of the ductus arteriosus complicated with *Streptococcus viridans* infection. It was believed unlikely that there was any additional congenital or acquired heart lesion. Because there was nothing of value to offer in the way of medical treatment, the idea of attempting to obliterate the patent ductus by surgical means had some appeal. After considerable discussion the matter was broached to the patient and her parents, and the operation undertaken with their full approval.

Operation was performed March 16, 1937. After exposure of the pulmonary conus and the root of the aorta the patent ductus was readily identified. It seemed approximately 1 cm. in length and 0.5 cm. in diameter. A strong thrill was felt when a finger was placed directly on the vessel. It could be occluded easily with digital pressure, and this had neither any appreciable effect on the heart's action nor did it alter the blood pressure. The ductus was freed by blunt dissection for about three-fourths of its circumference anteriorly, laterally, and mesially. How-

ever, the right pulmonary artery was so intimately bound to it by fibrous tissue that any effort to free the posterior portion seemed extremely hazardous. Consequently an attempt was made to obliterate the ductus with a series of plicating sutures. This resulted in a considerable reduction in the lumen of the vessel but obliteration was not complete. No attempt was made to evert and suture the pulmonary artery at the pulmonary opening of the ductus. The wound was closed without drainage.

The patient's postoperative course was remarkably uneventful till within an hour of her death. She continued to feel well until the evening of the fourth day when she suddenly vomited 200 c.c. of sour-smelling yellowish fluid and quickly became cyanotic and pulseless. The blood pressure could not be obtained. Gastric lavage was without beneficial result, and despite stimulation the patient died within an hour. The immediate cause of death was acute dilatation of the stomach.

Autopsy.—The post-mortem examination was limited to the thoracic contents. The wound was uninfected and there was no evidence of hemorrhage. The pleura was intact, and there was only a little pleural transudate. The lungs showed many scattered small infarcts; in the center of a few of the larger ones there was softening and necrosis. The heart weighed 220 gm. The pericardium, myocardium, and valves were normal. One centimeter above the right anterior leaflet of the pulmonic valve, the wall of the pulmonary artery presented a friable yellowish-gray papillary vegetation measuring about one centimeter in diameter (Fig. 1). A similar vegetation, 3 mm. in diameter, was situated at the pulmonary orifice of the ductus arteriosus which was patent and had a lumen approximately 3 mm. in diameter and a length of approximately 1 mm. The length of the ductus consisted almost entirely of the thickness of the walls of the aorta and pulmonary artery, which were contiguous at this point. The stomach, as seen through an incision in the diaphragm, was acutely dilated and occupied the greater part of the abdominal cavity.

DISCUSSION

It is of most interest to consider this case in the light of those conditions which must be fulfilled before there is any hope of cure. These conditions include accuracy in diagnosis, limitation of the bacterial lesions to the ductus and the immediately adjacent portion of the pulmonary artery, the feasibility of surgical intervention,* and recovery from operation.

The diagnosis of patent ductus arteriosus, when not associated with other congenital abnormalities, should ordinarily offer little difficulty. The continuous murmur with systolic accentuation, and the thrill, such as were observed in the present case, together with the x-ray evidence of dilatation and increased pulsation in the region of the pulmonary artery, make the diagnosis. However, in those instances where additional congenital cardiac abnormalities are present, the diagnosis may present difficulties.

*On May 6, 1907, in a paper³ before the Philadelphia Academy of Surgery, John C. Munro of Boston proposed ligation of the patent ductus arteriosus. He had made dissections on cadavers of newborn infants and proposed to split the sternum and to place a tie around the ductus or to crush it. Munro felt that the ductus was largely intrapericardial, and his operation approached it by opening the pericardium. So far as can be ascertained there is no record of his ever having attempted it on the living. He felt the operation was justifiable in cases of impending death from circulatory disturbances "with a reasonable basis for believing that the duct will be open."

If the bacterial vegetations are present in places other than in the immediate vicinity of the ductus, their removal or destruction is probably impossible. An exception to this may be the removal of vegetations from the pulmonary artery by means of a modified Trendelenburg operation. Unfortunately, a survey of the pertinent medical literature reveals only one instance⁴ in which the bacterial vegetations were limited to the pulmonary orifice of the ductus and only a few instances in which the lesions were limited to the ductus and the pulmonary artery. However, it must be remembered that these data represent the findings at death, and it is surely possible that for a considerable time before death the vegetations may be confined to the neighborhood of the patent ductus. Apparently the infection nearly always begins in relation to the pulmonary orifice of the ductus, often extending to the pulmonary valves, but rarely into the aorta.⁵ Hence a correct diagnosis must be made very early or there can be little hope of successful surgical intervention.

In the present case operation was not feasible because of the extensive bacterial vegetations in the pulmonary artery. The operation as performed would not even have allowed the destruction of the vegetations in the ductus itself. However, in any future attempt an effort should be made not only to obliterate the ductus itself but also the adjacent portion of the pulmonary artery. This procedure might be successful in removing all the vegetations from direct contact with the blood stream and in allowing the natural defense forces to kill the bacteria.

SUMMARY

1. Nearly one patient in four with patency of the ductus arteriosus dies because of subacute bacterial endocarditis or endarteritis.
2. In the case herein reported an attempt was made to destroy the bacterial vegetations by obliteration of the ductus.
3. The difficulties attending an operation of this nature are discussed.
4. In selected cases removal or obliteration of the patent ductus arteriosus should be attempted before the appearance of a serious degree of heart failure or subacute bacterial endocarditis or endarteritis.

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THE CLINICAL DIAGNOSIS OF TRICUSPID STENOSIS

CONFIRMATORY REPORT OF A CASE DIAGNOSED ANTE MORTEM*

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SAN FRANCISCO, CALIF.

IN A previous publication in the AMERICAN HEART JOURNAL¹ we discussed the clinical diagnosis of stenosis of the tricuspid valve, enumerating the various abnormal physiologic phenomena associated with this valvular defect, and presented a detailed report of a case in which the clinical signs of tricuspid stenosis were demonstrable. This follow-up report deals with the subsequent course of the patient's illness and the necropsy observations which substantiated the clinical diagnosis.

Clinical Course.—At the time of our previous report, the patient, a young married woman twenty-four years of age (No. U 2105), had been last seen in the Out-Patient Department May 26, 1935. At that time the clinical diagnosis was "chronic rheumatic heart disease with mitral stenosis and insufficiency; tricuspid stenosis and insufficiency; and cardiac hypertrophy and dilatation, functional Group IIb."

Earlier electrocardiographic studies had shown various arrhythmias, including paroxysmal nodal tachycardia, nodal rhythm, nodal ectopic beats, and auriculoventricular dissociation. Large notched P-waves in Leads I and II, and right axis deviation, had been present in all tracings showing normal rhythm. Auricular and ventricular hepatic pulsations had been consistently present except with nodal rhythm, when only the systolic pulsations had been demonstrable.

The patient had always been cyanotic and subject to dyspnea, particularly during attacks of nodal tachycardia, but she had never been orthopneic or edematous. Attacks of nodal tachycardia were satisfactorily prevented or controlled by the administration of quinidine sulfate.

From June 14, 1935, to Nov. 1, 1935, her course was uneventful except for two attacks of nodal tachycardia lasting from four to six hours, both of which were terminated promptly by a few additional doses of quinidine sulfate. During this period she performed her ordinary household duties despite advice to the contrary.

On Nov. 27, 1935, she was admitted to the University of California Hospital with an acute upper respiratory infection. Dyspnea and cough were quite bothersome, and cyanosis had increased somewhat. There was a slight elevation of temperature during the afternoon for the first three days, but none thereafter. Numerous coarse râles were heard over both lungs, but these had practically disappeared at the time of her discharge from the hospital, Dec. 4, 1935. An electrocardiogram made at this time showed the presence of auriculoventricular dissociation (she had had no digitalis) and roentgenologic studies indicated that the heart had increased in size in all dimensions since the last preceding examination. There was no roentgenographic evidence of pneumonia. Except for the arrhythmia which was present during auriculoventricular dissociation, physical examination showed no changes in the heart. The systolic and diastolic murmurs over the mitral and tricuspid areas were easily distinguished. The blood pressure was 100/88. Blood

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cultures were negative. It was thought that she had had a mild attack of congestive cardiac failure which had been precipitated by the acute upper respiratory infection.

The patient was seen again in the Out-Patient Department Feb. 7, 1936, at which time she was very uncomfortable. Her pulse rate was 168 per minute, and there was no arrhythmia. An electrocardiogram revealed the presence of nodal tachycardia. The dose of quinidine sulfate was increased to 0.4 gm. two or three times a day, and she was sent home and advised to stay in bed until her cardiac rate became normal. On February 28, 1936, when she was seen next, she told a story of having had, two weeks previously, a sudden attack of severe sharp pain originating between the scapulae and radiating bilaterally and anteriorly to the sternum and down both arms. She had been taken to the emergency hospital, where a "hypodermic injection" was administered, resulting in immediate relief of this distress. No cough, tachycardia, or increased dyspnea had accompanied this attack. On examination at this time she appeared thin and pale, and complained of severe dyspnea. The lungs were normal. The cardiac findings were unchanged; the heart rate was 104 per minute. The blood pressure measured 100/70. The liver was enlarged and tender. Double pulsations were plainly palpable in the liver and visible in the superficial cervical veins.

On March 30, 1936, she entered the University of California Hospital with the history of sudden onset of paralysis of the entire right side of the body several days after her last visit to the Out-Patient Department. She had been unconscious for twenty-four hours and had experienced motor aphasia for several days thereafter. The aphasia disappeared gradually, but weakness of the right side of her body persisted. Occasionally she had had cough with small quantities of blood-stained sputum. The degree of dyspnea had remained about the same.

On examination at this time she was found to have orthopnea and marked acrocyanosis. There was a right facial nerve palsy of the supranuclear type. The lungs were normal except for a few crepitant râles at both bases. The heart was enlarged both to the right and left. The left border of dullness in the sixth intercostal space was 14 cm. from the midsternal line, and the right border in the same interspace was 4 cm. from the midsternal line. A presystolic thrill was palpable at the apex. A low-pitched presystolic murmur and a louder high-pitched systolic murmur were heard at the apex. Over the lower portion of the sternum there was a well localized, short, high-pitched diastolic murmur, and a loud systolic murmur. The pulmonic second sound was accentuated. The heart was beating regularly at a rate of 90 per minute. The blood pressure measured 94/70. The edge of the liver was palpable 4 cm. below the right costal margin, and double hepatic pulsations were plainly palpable. The left arm and leg were normal, but a 30 to 50 per cent diminution of muscular power was present on the right side. Except for loss of the abdominal reflexes on the right side, all of the reflexes were normal. Examination of the urine and blood showed nothing abnormal.

An electrocardiogram made March 30, 1936, showed pronounced right axis deviation, with high, broad P-waves in Leads II and III, notching of the P-wave in Lead I, and diphasic T-waves in Leads II and III. The mechanism was normal, and the rate was 83 a minute. Electrocardiograms made April 6 and 10, 1936, showed very little change except for slowing of the rate and the irregular appearance of premature nodal beats. Simultaneous electrocardiograms and hepatic pulse tracings which were obtained April 10, 1936 (Fig. 1), at a time when ventricular ectopic beats were numerous, showed that the latter produced no auricular wave in the hepatic pulse.

Roentgenologic studies disclosed progressive enlargement of the transverse diameter of the heart, and great enlargement of the right auricle (Fig. 2). There was considerable pulmonary congestion, but no evidence of pleural effusion.

The patient was kept in bed and treated with quinidine sulfate. She showed remarkable improvement during her stay in the hospital and was discharged April 12, 1936.

She was seen again Aug. 21, 1936. At this time she was feeling very well and had gained 10 pounds since she left the hospital. There were no significant signs

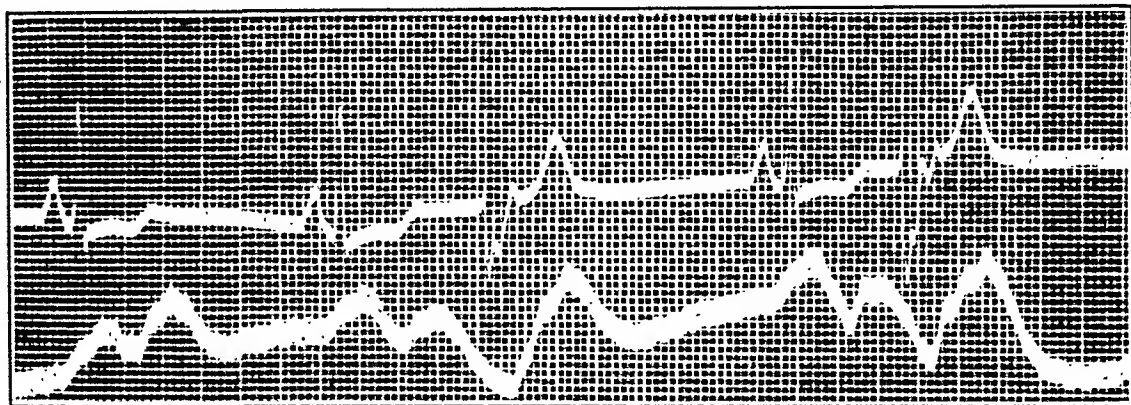


Fig. 1.—Simultaneous electrocardiogram (Lead II) and hepatogram illustrating the disappearance of the auricular wave in the hepatic pulsations during ventricular extrasystoles.

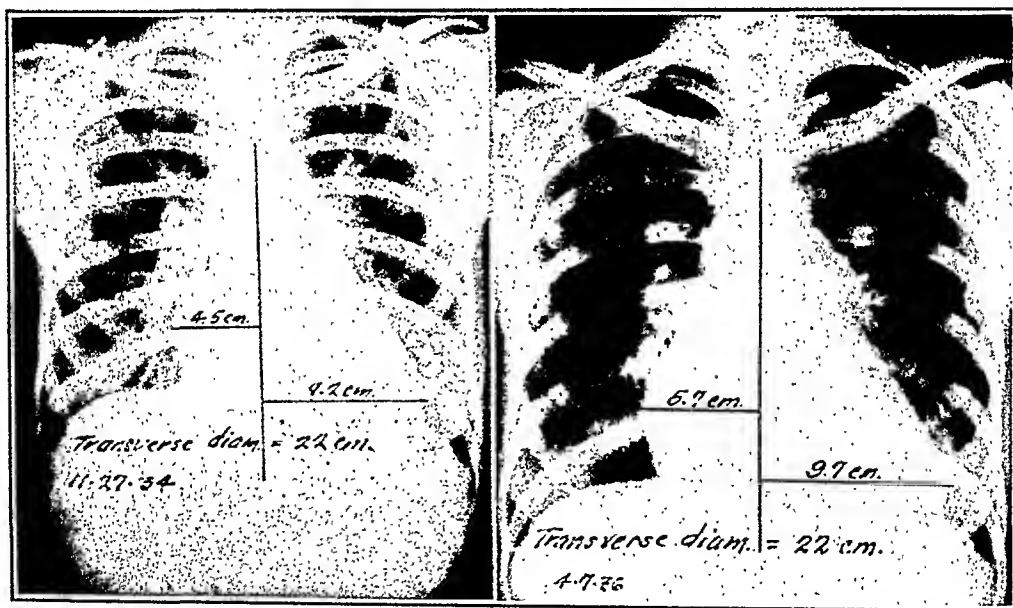


Fig. 2.—Roentgenograms illustrating the progressive increase in the transverse cardiac diameter, with marked enlargement of the right auricle.

of the previous hemiplegia, and she had experienced rapid heart action only once since her last examination. On Jan. 8, 1937, she reported again to the Out-Patient Department, stating that she had been getting along unusually well, although she had lost several pounds in weight. There were no changes in the physical findings.

On Jan. 28, 1937, the patient died at home of lobar pneumonia. Permission to make a post-mortem examination of the chest and thoracic organs was obtained.

*Necropsy Observations.**—Upon removal of the breast plate, the mediastinum was seen to be shifted slightly to the right.

*By Dr. James F. Rinehart, of the Department of Pathology, University of California Medical School.

Each pleural cavity contained approximately 200 c.c. of fluid. The lungs were crepitant except at the bases; the lower lobe of the right lung was consolidated. The lower lobe of the left lung showed very little that was abnormal. Microscopic examination of the parenchyma of the right lower lobe revealed changes typical of lobar pneumonia in the stage of red hepatization. There were no noteworthy changes in the left lung.



Fig. 3.—The post-mortem appearance of the tricuspid and mitral valves viewed from the right and left auricles, respectively.

A, tricuspid valve.

B, mitral valve.

The pericardium was considerably infiltrated with fat, and the cavity contained about 60 c.c. of clear yellow fluid, but there were no adhesions.

Prior to removal, the heart measured 15 cm. from its right to its left border. The left border was approximately at the left anterior axillary line, and the right

border extended about 4 cm. to the right of the midsternal line. The entire organ was dilated, but weighed, despite the obvious enlargement, only 350 gm. The auricles were twice the normal size and moderately hypertrophied. The average thickness of the auricular wall was 1 cm. The myocardium was firm, and the right ventricle was hypertrophied and dilated. The wall of the right ventricle measured 7 mm. in thickness, and that of the left, 14 mm. There was a small area of fibrosis in the apical portion of the right ventricle just beneath the epicardium. Additional areas of fibrosis were seen in the region of the auriculoventricular node immediately above the tricuspid valve and around the sinoauricular node. The leaflets of the tricuspid valve were fused and thickened, with verrucous granulations studding the line of closure. The valve was incompetent and moderately stenotic. Its circumference measured 11.5 cm. at the base and 8.2 cm. at the line of closure (Fig. 3). Thickening and fibrosis of the mitral valve had reduced its orifice to a rigid crescentic buttonhole about 1.5 cm. in diameter and 5 cm. in circumference (Fig. 3). The left ventricle was slightly dilated, and its wall was only slightly thicker than that of the right ventricle. The aortic valve measured 5 cm. in circumference and showed a very slight diffuse thickening but did not appear to be significantly affected by the rheumatic process. One of the aortic leaflets was fenestrated in its lateral margin. The pulmonary valve was not grossly abnormal; it measured 7 cm. in circumference. The chordae tendineae were thickened, partly fused, and shortened. The papillary muscles were both hypertrophied and flattened. The aorta showed scattered, slightly elevated yellowish atheromatous nodules extending from the valve to the arch. The coronary vessels were patent and elastic. There were no auricular thrombi. (This is of interest because the hemiplegia, which this patient had had several months before death, had been attributed to the loosening of a left auricular thrombus.)

Histologic examination of the myocardium showed areas of fibrosis with a few small round cells and plasma cells. The fibrosis in the right ventricle extended into the endocardium, which appeared somewhat thickened.

There was considerable edema of the tricuspid valve with much chronic inflammatory cellular infiltration at its base. In the free portion of the valve there were numerous small hemorrhages and several fairly limited areas of round cell infiltration with fibrosis and hyaline degeneration. The rheumatic process was relatively active in the tricuspid valve, as evidenced by a proliferative valvulitis and a recent hyaline verrucous lesion at the closure line. Sections of the mitral valve presented a similar appearance except that there was greater degeneration of the connective tissue with evidences of hyalinization and calcification.

Because of the various nodal arrhythmias which this patient had had, sections were taken from the region of the auriculoventricular node; they showed a mildly active rheumatic involvement of the auricular endocardium. There were a few small Aschoff bodies in the adjacent cardiac musculature.

SUMMARY

This supplementary report covers the later clinical course and autopsy findings in a case of acquired tricuspid stenosis in which the diagnosis was made ante mortem and confirmed by autopsy.

REFERENCE

1. Friedlander, R. D., and Kerr, W. J.: The Clinical Diagnosis of Tricuspid Stenosis; Report of a Case Complicated by Paroxysmal Nodal Tachycardia and A-V Dissociation, *AM. HEART J.* 11: 357, 1936.

Department of Reviews and Abstracts

Selected Abstracts

Opitz, E., and Smyth, D. H.: *Blood Flow Through the Kidney During Stimulation of the Carotid Sinus.* Arch. f. d. ges. Physiol. 238: 633, 1937.

As a supplement to the studies of Hartmann, Orskov, and Rein (abstract AM. HEART J., Vol. 13, p. 385, 1937) the blood flow to the kidneys was studied in dogs during stimulation of the carotid sinus nerves before and after denervation. In spite of the fall in systemic blood pressure, the flow of blood through the kidneys remained relatively constant in contradistinction to that through the fore leg, where it was increased. This was true after denervation of the kidney as well as before. An example of the automaticity of regulation of blood flow to the kidney, which is independent of its nerves, is demonstrated. Records of simultaneous curves of blood flow (Rein stromuhr) through renal vein and brachial artery and systemic arterial pressure are reproduced.

STEELE.

Springorum, W.: *Regulation of the Circulation in Skin Influenced by Local Heat.* Arch. f. d. ges. Physiol. 238: 644, 1937.

Using his previously developed technique of measuring blood flow to the skin by means of a Rein stromuhr placed upon the auricular artery of a dog, Springorum shows that vasodilatation by local heat does not alter the effectiveness of adrenalin. From this fact he concludes that an acetylcholine-like substance is not responsible for vasodilatation due to heat. The argument is reinforced by the fact that neither acetylcholine nor histamine gives rise to further increase in blood flow when the arterioles are already dilated by local heat. He concludes further that the blood flow during local heat is not governed by the rate of metabolism.

STEELE.

Bacq, Z. M.: *Studies on the Physiology and Pharmacology of the Autonomic Nervous System: XXV. The Rôle of the Liver and Abdominal Viscera in the Destruction of Adrenalin.* Arch. internat. de physiol. 45: 1, 1937.

The effect of injecting identical amounts of adrenalin into the crural veins of cats upon contraction of the nictitating membrane or of the virgin uterus was recorded on smoked drums before and after evisceration and before, during, and after arrest of the circulation to the viscera. The degree of contraction was either unchanged or so little increased after either procedure that the increase could be ascribed to reduction of the cellular mass through which the adrenalin was distributed. The author concludes, therefore, confirming the work of Markowitz and Mann, that the viscera play no rôle in the destruction of adrenalin in vivo.

STEELE.

Enger, R., Gerstner, H., and Sarre, H.: *Dependence of Renal Blood Flow Upon Ureteral Pressure.* Zentralbl. f. inn. Med. 58: 865, 1937.

Ureteral pressure was induced in anesthetized dogs by cannulating the ureter and leading the tube therefrom into a graduated cylinder in which any desired atmospheric

pressure could be obtained. Optical records of simultaneous tracings of arterial pressure, renal blood flow (Rein stromuhr), and ureteral pressure during the procedure were made.

Eight successful experiments were performed. Only slight, perhaps negligible, changes in renal flow occurred below 40 to 60 mm. Hg. From there on up, decrease in blood flow was rapid, falling frequently to one-third of the original value at ureteral pressures of 120 mm. Hg. Urine ceased to flow at from 40 to 70 mm. Hg. When urine secretion was allowed to take place against a manometer, without artificial increase in pressure, it was within this range of pressure (40 to 70 mm. Hg, usually about 60) that urine flow ceased. The authors note that this pressure is just at the point at which renal blood flow begins to decline and suggest that ureteral obstruction in patients may interfere with the blood flow.

It is interesting to note that in the two records produced, the arterial pressure rose slightly in one and fell abruptly in the other.

STEELE.

Menne, Frank R., Beeman, Joseph A. P., and Lobby, Daniel H.: Cholesterol-Induced Arteriosclerosis in Rabbits, With Variations Due to Altered Status of Thyroid. *Arch. Path.* 24: 612, 1937.

Rabbits fed pure cholesterol over a long period under different conditions, namely, (a) under normal conditions (controls), (b) following thyroidectomy and reduction in metabolism, as well as after administration of iodine to inhibit thyroid function, and (c) during administration of desiccated thyroid in such a manner as to produce intermittent periods of progression and regression in metabolism, all acquired atherosclerosis in varying degrees. In the rabbits under normal conditions, but to a greater extent in the rabbits with a depressed metabolic rate (due to removal of the thyroid or to administration of compound solution of iodine) the production of such lesions was readily accomplished. The authors conclude that the results tend to corroborate the major contention of Leary, that there are two primary conditions necessary to the development of atherosclerosis, (a) an excess of cholesterol or cholesterol esters in the blood and (b) the stress due to mechanical factors in the circulation.

MONTGOMERY.

Konschegg, T., and Monauni, J.: Quantitative Measurements of the Adrenalin Content of the Vasopressor Substance. *Ztschr. f. klin. Med.* 131: 99, 1936.

The authors found that adrenalin can be split off from the vasopressor substance obtained from blood and colorimetrically determined. In renal hypertension it was found that the content of adrenalin obtained in this way was markedly increased. In essential hypertension the adrenalin values were only slightly higher than in normals.

KATZ.

Petersen, H.: Rhythmic Spontaneous Contractions in Vessels. *Ztschr. f. Biol.* 97: 378, 1936.

The spontaneous contraction in isolated vessel strips is a reaction to stretch. In an isolated artery, the sudden increase of pressure by 70 mm. Hg is followed 1.6 seconds later by a further increase in pressure which seems to be in the nature of a response to the stretch stimulus.

KATZ.

Petersen, H.: Electrical Changes Recorded From Arterial Strips of Mammal. *Ztschr. f. Biol.* 97: 393, 1936.

Electrical records are obtained in such isolated arteries when they are contracting rhythmically. The electrical evidence precedes the mechanical by 8 to 10 seconds and lasts 30 seconds. They have a magnitude of 0.5 to 3 millivolts.

KATZ.

Gremels, H.: Disturbances of the Energetics of the Mammalian Heart. *Arch. f. exper. Path. u. Pharmacol.* 182: 1-54, 1936.

Continuous infusion of insulin and glucose causes a massive and long lasting decrease in oxygen consumption and with it an increased efficiency of the heart. Acetylcholin also has a similar effect which is aided by the bradycardia. Adrenalin and sympatol increase work and make the heart more efficient. Small doses of adrenalin inhibit oxygen consumption.

KATZ.

Battro, A., and Lanari, A.: Injection of Acetylcholine Into the Carotid Artery of Man. *Compt. rend. Soc. de biol.* 125: 541, 1937.

Acetylcholine was injected into the common carotid artery of seventeen individuals. No untoward accidents occurred. The injection was followed by a remarkable series of events: (1) immediately by hyperpnea and sometimes cough lasting one-half to one minute, (2) then by the nervous phenomena of motor agitation with occasional deviation of the eyes to the side opposite the injection, also lasting about a minute, (3) by homolateral vasodilatation of the face, neck and conjunctivae lasting from ten to fifteen minutes, (4) inconstant bradycardia and in three cases transient auricular fibrillation, neither of which occurred if atropine had been previously injected, (5) homolateral myosis, sweating, and lacrimation. He discusses briefly the site of action of the drug in eliciting the various phenomena.

STEELE.

Wezler, K., and Goyert, KL: A Method for Testing the Function of the Carotid Sinus Mechanism. *Ztschr. f. Kreislaufforsch.* 29: 241, 1937.

A new procedure for estimating the function of the carotid sinus nerves in man is described. The measures of degree of function are obtained from simultaneous records of pulse waves from the carotid, radial, and femoral arteries and consist of the following: 1. The duration of the basic period of oscillation of the carotid artery, a function which increases with decrease in pressure within the artery, is taken as a measure of degree of stimulation of the pressor receptor nerves. 2. The ratio of the velocity of the pulse wave in the muscular arteries (for the most part brachio-radial) to the aorta is taken as a measure of the degree of contraction of the smooth muscle of the arteries. 3. The ratio of duration of systole to the interval between pulse beats is taken as an estimation of the reflex action upon the heart. For varying the degree of carotid sinus stimulation the authors vary position of the individuals studied from lying to upright. It is interesting to note that the velocity of the pulse wave in the muscular arteries as compared with that in the aorta is much greater when the individual is standing than when the individual is lying down.

In previous work Wezler has developed the thesis that contraction of the muscular coat of an artery makes the arterial wall more distensible, i.e., reduces the velocity of the pulse wave. On the basis of this theory he concludes from the present study: (1) With decrease in carotid pressure, inferred from the decreased frequency of the basic oscillation of the wall, the smooth muscle of the muscular arteries contract,

(2) and the ratio of systole to the interval of the pulse as well as the frequency of the pulse increases. From these two conclusions he draws the inference that a high degree of arterial sympathetic tone is associated or bound up with a high degree of vagal or parasympathetic tone.

STEELE.

Moon, Virgil H.: Shock, Its Mechanism and Pathology. Arch. Path. 24: 794, 1937.

Shock is a circulatory deficiency, not cardiac and not vasomotor in origin, characterized by decreased total blood volume, decreased volume flow and by hemoconcentration. An imposing array of evidence from diverse sources supports the interpretation that substances absorbed from injured tissue produce progressive circulatory deficiency by their effects on the minute vessels in systemic areas. Under the influence of these substances, and of other agents, the capillaries and venules become atonic and dilated, and their walls become abnormally permeable to the fluids of the blood. This results in stasis and leakage of fluid from the vessels. It also increases the volume capacity of the vascular system, reduces the total volume and the volume flow of the blood, increases its concentration, and produces edema. The evidence does not support the idea that local loss of blood and/or fluid at the site of injury is an adequate explanation for shock. But such a loss of fluid is a factor. It contributes to the circulatory deficiency in proportion to the volume of blood and fluid lost.

MONTGOMERY.

Hadorn, W.: Effect of Insulin and Hypoglycemia on the Heart (as Shown in Schizophrenic Patients Treated With Insulin). Ztschr. klin. Med. 130: 643, 1936.

This study is based on 43 schizophrenics without heart disease, who received large doses of insulin. During hypoglycemia, there occurred tachycardia, blood pressure rise, arrhythmias, and electrocardiographic changes. The electrocardiographic changes consisted of S-T depression, flattening or inversion of T, and prolongation of QRST and of the QRS complex. These heart changes are reversible; hence the author believes that there is no permanent heart damage from the insulin treatment.

KATZ.

Enger, R., and Arnold, H.: The 1:2-Nitrosonaphthol Reaction in Hypertensive Patients and Persons With Normal Blood Pressure: I. Blood Studies. Ztschr. f. klin. Med. 130: 725, 1936.

A negative nitrosonaphthol reaction was obtained in specially treated blood in normals, in essential hypertension, in amyloid nephrosis with marked renal insufficiency, and in acute nephritis. A positive reaction was found in chronic hypertensive nephritis and in malignant nephrosclerosis.

KATZ.

Rich, Arnold R., and Duff, G. Lyman: The Production of Hyaline Arteriosclerosis and Arteriolonecrosis by Means of Proteolytic Enzymes. Bull. Johns Hopkins Hosp. 61: 63, 1937.

Arteriolar lesions having the characteristics of hyaline arteriosclerosis occur at the site of injection of tryptic enzymes of animal or plant origin into the subcutaneous tissues of normal dogs. Previous medial hypertrophy or intimal proliferation is essential for the production of these changes. Whether the enzymes act directly upon the vessel wall or whether the lesion results from the action of products of protein decomposition is at present undetermined.

HINES.

Ludwig, H.: Experiments on Hydromechanics and Hemodynamics: IX. Pulse Wave Velocity in Health and Disease. *Ztschr. f. d. ges. exper. Med.* 99: 352, 1936.

Because of variability in pulse wave velocity, studies must be based on a large series of observations. The author used a Müller electrical transmitting carbon capsule and determined carotid-femoral and carotid-brachial transmission times. The velocity in the arm vessels (carotid-brachial) and the aorta (carotid-femoral) increase with age. After the age of 50 years the aortic pulse wave velocity accelerates faster than that of the arm vessels. The deviations in the readings from average at any age group is as high as 50 per cent, the mean deviation being 18 per cent. On the average, pulse wave velocity tends to increase with cardiac acceleration and elevation of diastolic blood pressure. In hypertension the carotid-femoral pulse wave velocity becomes very high (maximum value 22.2 m./sec.). The acceleration is greater in essential than in renal hypertension, indicating marked alterations in the aorta in essential hypertension. In heart insufficiency the pulse velocity decreases.

KATZ.

Hecht, H., and Korth, C.: The Q-T Interval of the Electrocardiogram. *Ztschr. f. Kreislaufforsch.* 29: 577, 1937.

The Q-T interval represents the duration of the excited state of the heart and is related to the duration of the heart cycle. Its duration is not always related to mechanical systole. In 24 patients with tetany and very low Ca content the duration of Q-T is lengthened. This can be reversed by calcium injections. In one case with high calcium content (ostitis fibrosa generalisata) the Q-T interval was shortened. In normal individuals Q-T is shortened by calcium injections.

KATZ.

Hollmann, W., and Hollmann, H. E.: New Electrocardiographic Methods of Investigation. *Ztschr. f. Kreislaufforsch.* 29: 465, 1937.

The authors describe two methods of evaluating the variable factors that influence the electrocardiogram, viz., (1) the heart's position in the body, (2) the rotation of the electrical vector during the heart cycle, and (3) the distortion of the electrical axis by the relative muscle mass of the two ventricles. The first method consists in recording the "absolute cardiogram" which registers the changes of potential without regard to the direction of the potential. This can be done either for the frontal plane mapped by the standard three leads or for the three dimensional currents. This can be done by mathematical handling of the potentials of the several leads or by an integrating device. In this way, they have shown that the potentials registered during the heart cycle are all in one direction, the small initial and final deflection being merely the result of the direction assumed by the electrical axis when they are registered.

The second method consists in obtaining the actual record of the vector written by the resultant potential developed during the heart cycle. For this purpose a special cathode ray oscillograph was designed with six instead of four pole pieces (60° apart) to control the direction of the electron stream writing on the fluorescent screen. Each lead, I, II, and III, activates a pair of these pole pieces (180° apart). The result is a standing wave, which can be photographed and which gives the spatial value of the moving vector during the heart cycle. This they call the "triograph." By having moving instead of stationary film, a time record of the triogram is obtained from which the direction of rotation of the triogram can be determined.

KATZ.

Burkhardt, Edward A., Eggleston, Cary, and Smith, Lawrence W.: *Electrocardiographic Changes and Peripheral Nerve Palsies in Toxic Diphtheria*. *Am. J. M. Sc.* 195: 301, 1938.

Serial electrocardiograms were made on 140 patients showing evidence of toxic diphtheria; 28 of these showed changes in the contour of the electrocardiograms.

The electrocardiographic changes were divisible into two groups comprising (a) alterations in the T-wave and (b) alterations in the conduction system.

Twenty-three patients showed the T-wave changes occurring between the fifth and thirty-ninth day of illness. A majority of the changes occurred between the eighth and fifteenth day of illness.

Seventeen patients showed conduction changes between the fifth and thirteenth day of illness; 11 of these patients developed A-V dissociation. This complication invariably proved fatal.

Fourteen patients showing electrocardiographic changes died of toxic diphtheria; seven of these received large doses of diphtheria antitoxin on or before the fourth day of illness. Early administration of antitoxin did not save this group of patients.

Peripheral nerve palsies occurred in 65 per cent of the patients presenting electrocardiographic changes. The paralysis apparently bore no causal relationship to the cardiac phenomena.

There was a rough parallelism between the conductivity as shown by the electrocardiogram and the microscopic changes in the myocardium as demonstrated in the seven cases of this series that were autopsied.

The essential histologic changes in the myocardium due to toxic diphtheria are shown to be progressively, edema, congestin, cellular infiltration, degenerative changes in the muscle fibers, and ultimate fibrosis.

These lesions found at autopsy suggest that diphtheria may be one of the causes of chronic fibrous myocarditis in patients who survive the more toxic state.

The electrocardiographic findings constitute an important guide in the treatment of diphtheria. Complete inactivity is recommended for those showing abnormal electrocardiograms until the electrocardiogram has had ample opportunity to return to normal.

AUTHOR.

Ostrowski, W., and Pines, I.: *Electrocardiographic Changes in Pericardial Tamponade*. *Ztschr. f. d. ges. exper. Med.* 101: 465, 1937.

A parallelism between the electrocardiographic changes and the degree of pericardial effusion was found in experimental tamponade. The electrocardiographic changes are characteristic. The S-T segment is depressed and T becomes inverted. Cardiac ischemia is produced only when the effusion is rapid and large, but there always is interference with the inflow to the heart.

KATZ.

Herkel, W., and Weber, A.: *Clinical and Experimental Studies of the Electrocardiogram. IX. Course of the Action Potential on Chest Wall*. *Ztschr. f. klin. Med.* 131: 603, 1937.

The authors found that after the Q portion of QRS the greatest negativity on the thorax anteriorly is near the middle of the base of the heart. Then it rapidly spreads toward the right base and anterior wall of the right ventricle. Invasion ends first

in the middle of the heart. It takes place then in the following order: apex, right base, and, last, middle of the base. This is based on simultaneous recording of six leads by means of amplifiers and oscillographs.

KATZ.

Hegglin, R., and Holzmann, M.: Clinical Significance of Prolonged Q-T Interval. *Ztschr. f. klin. Med.* 132: 1, 1937.

Electrical systole was correlated with cycle length. In one group with prolonged Q-T, a decreased serum calcium was found, viz., tetany, spasmophilia, uremia, hepatic coma, and sprue. In this group there was a regular prolongation of Q-T when the calcium in the serum was below 9 mg. per cent, and a return to normal duration was indicated when the calcium content rose.

A second group of prolonged Q-T was found without a decreased calcium content. In this group there were (a) hypertrophied hearts on a hypertension basis and myocardial infarction, (b) diphtheria, pneumonia, and tuberculosis, and the Q-T prolongation was a sign of a serious outlook, (c) diabetic and hypoglycemic coma, (d) disturbances like myxedema, hyperadrenalemia with adrenal cortical tumors, or (e) some instances of lung emboli.

In the group with a lowered calcium content, prolongation of Q-T occurred involving chiefly the S-T interval; in the nonhypocalcemic group there was primarily a broadening of T. The latter form is the more serious, the authors believe.

KATZ.

Weber, A.: Clinical and Experimental Studies of the Electrocardiogram. X. The Meaning of the Electrocardiogram. *Ztschr. f. klin. Med.* 132: 153, 1937.

The author points out that in man one really never gets a unipolar lead since the chest electrode is removed from the heart; even on the heart one gets a potential difference of two electrodes. The potential on the surface of the body is about one-sixtieth of that on the surface of the heart. The small size of the deflection on the surface of the body is not due to a drop in the potential from the center to the periphery, but is an expression of the small potential differences between various spots on the body surface. Evidence is given to show that S-T and T depression is due to damage to one ventricle.

KATZ.

Barber, Hugh: Trauma of the Heart. *Brit. M. J.* Feb. 26, p. 423, 1938.

The forms of heart disease which have been recorded as the result of direct violence to the chest wall or as the result of strain are discussed. The conclusion is drawn that the physical signs on examination are of little assistance in assessing the diagnosis of trauma. Reliable clinical histories, in the widest sense of those terms, must be assessed with judicious care. This includes such evidence as the patient's own doctor can supply.

The clinical diagnosis of a contusion of the heart is discussed.

It is claimed that there is clinical evidence that the normal heart may become diseased as the direct result of overstrain from effort.

With regard to these two conditions, contusion of the heart and primary cardiac overstrain, it is difficult to obtain the proof that the symptoms in question are due to a genuine heart disability, but the probabilities in some cases are sufficient to justify the diagnosis.

AUTHOR.

Bacal, H. L., and Struthers, R. R.: The Organization of a Rheumatism Service. *Canad. M. A. J.* 38: 227, 1938.

The organization, both medical and physical of the "rheumatism" service in the Children's Memorial Hospital, Montreal, is described. The benefit both to the staff and to the patients of continuous observations by one group interested in a study of this disease is obvious. Of these benefits, one of the most marked is the freedom from repeated respiratory tract infections enjoyed by a moderately isolated group in a humidified atmosphere.

From these observations it may be concluded that the next advance in the study of rheumatic disease in childhood must come from the study of the bacteriology of this affection.

AUTHORS.

McEwen, Currier: Cytologic Studies on Rheumatic Fever. III. A Comparison of Cells of Subcutaneous Nodules From Patients With Rheumatic Fever, Rheumatoid Arthritis and Syphilis. *Arch. Path.* 25: 303, 1938.

The predominant cells of syphilitic subcutaneous nodules differed strikingly from those of rheumatic and rheumatoid arthritic nodules in their reaction to supravital staining and proved to be the distinctive stimulated monocytes and clasmotocytes previously shown to be characteristic of syphilitic lesions. Thus cytologic proof is added to the evidence provided by ordinary histologic study that the clinically similar subcutaneous nodules of rheumatoid arthritis and syphilis are pathologically dissimilar; the latter are shown to be not merely nonspecific lesions but representative of syphilitic tissue reactions in general. This result gives indirect support to the belief that in rheumatic fever, too, the subcutaneous nodules are characteristic of granulomas elsewhere in the body and that conclusions drawn from a study of cells of the nodules are applicable also to those of the cardiac lesions.

In contrast to the findings in the syphilitic lesions, the cells of nodules from patients with rheumatoid arthritis were in all essential features the same as those of orthodox rheumatic nodules. Obviously, this does not prove the identity of rheumatic fever and rheumatoid arthritis, but it does add one more bit of evidence to the clinical and histologic similarities suggesting a relationship between these two diseases, and, when taken into consideration with other histologic features, it indicates that at least in the proliferative phase of the tissue reaction they are similar.

A comparative study is reported of supravital stained preparations of subcutaneous nodules from patients with rheumatic fever, rheumatoid arthritis, and syphilis. The cells of rheumatoid arthritic nodules were found to have essentially the same characteristics as those of rheumatic fever. The cells of syphilitic nodules differed and proved to be those characteristic of syphilitic lesions in general.

AUTHOR.

Kaump, Donald H., and Dry, Thomas J.: Pulmonary Arteriolar Sclerosis. *Arch. Int. Med.* 61: 1, 1938.

Arteriolar sclerotic changes in the pulmonary arterial tree are more effective in producing right ventricular hypertrophy than are sclerotic changes in the larger parts of the pulmonary arterial tree. In all except three of the sixteen cases in which only the pulmonary artery and its main branches showed atherosclerotic changes, hypertrophy of the right ventricle was absent. Of thirteen cases in which there were varying degrees of diffuse pulmonary arteriolar sclerosis, hypertrophy of the right

ventricle was present in eleven. Hypertrophy of the right ventricle is, in these cases, probably an indication of elevation in blood pressure within the pulmonary artery. A close analogy exists between pulmonary arterial hypertension and peripheral arterial hypertension, in that sclerosis of the arterioles is a more common accompaniment of hypertension than sclerosis of arteries is.

MONTGOMERY.

Bonnet, B., and Bonamour, G.: Periodically Recurrent Hemorrhages of the Vitreous in Arterial Hypertension at the Time of the Menopause. *J. de méd. de Lyon*, No. 413: 177, 1937.

Three cases of long-standing arterial hypertension are reported with development of difficulty in vision at the onset of, and during, the menopause, due apparently to hemorrhages into the vitreous humor. Associated arterial changes were usually noted in the retina and elsewhere. The three reported cases were over fifty years of age, but the authors make the statement that this syndrome is also seen following artificial menopause at an earlier age.

STEELE.

Scheid, G., and Stern, A.: Transcerebral Iontophoresis of Bee Poison in Arterial Hypertension. *Klin. Wchnschr.* 33: 609, 1937.

Proceeding on the theory that narrowing of the arteries to the vasomotor centers and consequently reduction in blood flow may be the cause of hypertension the authors believe that falls in arterial pressure obtained in hypertensive patients even up to twenty-four hours after treatment were due to the dilating effect on the cerebral vessels of bee poison introduced by transcerebral iontophoresis. The current used was from 2 to 5 Ma. for fifteen minutes driven from forehead to nape of neck from lead electrodes.

STEELE.

Oppenheimer, Enid Tribe, and Prinzmetal, Myron: Rôle of the Arteries in the Peripheral Resistance of Hypertension and Related States. *Arch. Int. Med.* 60: 772, 1937.

A study was made of the brachial-digital pressure gradient for subjects with low, normal, and high blood pressure. Similar studies were also made for the patient with paroxysmal hypertension due to adrenal pheochromocytoma and for four patients with obstructive vascular disease. The average brachial-digital pressure gradient for patients with chronic hypertension was found to be approximately the same as for those with a normal or a low blood pressure. For three patients with very high blood pressures, there was a notable reduction in gradient. Since there is no increase in the gradient in hypertension, it is concluded that there is no increased resistance in the arteries larger than the digital arteries. For the patient with pheochromocytoma with epinephrinemia the pressure gradient was markedly increased, indicating constriction of arteries larger than the digital arteries. For four patients with obliterative vascular disease the pressure gradient was also increased, owing to obstruction in the arteries resulting from organic changes. This increase in pressure gradient, contrasted with the normal or perhaps decreased gradient of chronic hypertension, supports the view that in hypertension there is no increased resistance in the larger arteries.

MONTGOMERY.

Stalker, L. K., and Pemberton, J. deJ.: Arteriovenous Fistula: Report of a Case. Proc. Staff Meet., Mayo Clinic 12: 557, 1937.

A case of acquired arteriovenous fistula in a boy, 15 years of age, is presented. There was marked hypertrophy of the leg on the affected side, which is unusual in arteriovenous fistula of the acquired type. There was occlusion of the femoral vein by an organized thrombus just proximal to the fistulous communication which impaired the return flow of blood and resulted in marked venous engorgement of the limb. The fistula was treated by ligation of the vessels above and below the fistulous process, and excision of the segment of artery and vein including the fistulous tract.

HINES.

Allen, E. V., and McKechnie, R. E., Effect of Intermittent Occlusion on the Circulation of the Extremities. J. Lab. & Clin. Med. 22: 1260, 1937.

A study of the effects of intermittent venous occlusion on the skin temperatures of nineteen patients with or without occlusive arterial disease did not disclose evidence of significant or consistent vasodilatation resulting from the procedure.

AUTHOR.

Miura, O.: Concerning a Poisonous Mushroom "*Clitocybe acromelalga*" Ichimura and the Disease Similar to Erythromelalgia Produced by It. Tohoku J. Exper. Med. 31: 1, 1937.

Three cases are reported in which redness, sensations of pricking, tickling, and eventually pain in the extremities followed ingestion of mushrooms (*Clitocybe acromelalga*). Exposure to cold or heat increased the various sensations. One patient recovered in approximately ten days. The second, a sickly individual from childhood, developed edema, pustular eruptions, and ulcers of the legs, after the initial symptoms of burning and redness, and died apparently about one month after eating the mushrooms. In the third patient, too, edema and ulceration of the skin of the feet, with loss of sufficient tissue to necessitate skin grafts, followed the original redness and pain, but he eventually recovered. Histologic study of skin from this individual showed massive edema of the papillary layer and extreme widening of the papillary and subpapillary vessels, which were filled to bursting with blood. Mild thickening of the epidermis and considerable increase in pigmentation of the basal cells were also noted.

Perhaps the most interesting observation was the marked polycythemia which developed in the two cases in which counts of the red blood cells were made. One reached a level of 10.26 millions on the ninth day following the ingestion of the mushrooms and fell off by the thirteenth day to 5.56 millions. The maximum in the second case was 7.1 millions on the sixth day.

The pharmacologic action of the mushroom is then discussed, and its similarity to ergot is pointed out. The disease produced in man by its ingestion is likened to Weir Mitchell's disease (erythromelalgia), but the author makes clear that in the former the patient recovers while the latter is a chronic affliction. Because in one case local anesthetization of the nerves was followed by improvement, he believes that the disturbances of the circulation are due to the effects of the plant upon the vasomotor nerves.

STEELE.

Yater, Wallace M.: Maintenance of the Functional Integrity of Occluded Large Arteries as Demonstrated by Thorotrast Arteriography. *Am. J. M. Sc.* 194: 372, 1937.

Arteriography is teaching us many things about the mechanics of the circulation in vascular disease which are not demonstrable otherwise. In Case 1 we see how nature restored the function of a main artery by sidetracking the blood from above an occluded portion of the artery through a branch and bringing it back to the main trunk below. Undoubtedly other collateral arteries aided in this restoration. The history suggests embolism, but more probably sudden thrombosis occurred. The restorative alterations were made within a month of the time of occlusion.

Case 2 is quite different from Case 1. Here the occlusive process apparently developed very slowly, being due to gradual diminution of the lumen by atherosclerosis. But again we see the same detour of the blood through smaller arteries back to the main artery. Case 3 was similar to Case 2 in that the occlusive process was undoubtedly a very slow one due to atherosclerosis.

Readjustment of the circulation of the lower extremity by direct anastomosis allows one to make a better prognosis than in cases in which the main arteries are completely obliterated and in which the circulation is entirely dependent upon smaller vessels. In Cases 1 and 3 there was no gangrenous process, and in Case 2 trophic changes were minor and healed readily.

In cases of embolism in which recovery ensues, it may be that the circulation in an extremity is reestablished in the manner described, at least at times. Arterectomy as advocated by Leriche may be efficacious in that such a procedure conceivably may stimulate the development of direct anastomoses as well as the collateral circulation in general.

Only one illustration of a case similar to these could be found in the literature. This was Case 20 (p. 377) of Demel, Sgalitzer and Kollert. It is probable, however, that such cases have been observed in large clinics where arteriography is frequently employed.

It is believed that most collateral vessels are merely enlarged and elongated branches that existed prior to the onset of vascular disease. Such cases as those described indicate that at times new anastomoses may develop, however, since it is quite improbable that a branch of an artery normally empties into the same artery a short distance below its origin.

AUTHOR.

Cust, Norman: Symmetrical Peripheral Gangrene Following Scarlet Fever. *M. J. Australia* 2: 880, 1937.

A single case is presented. A two-year-old boy developed gangrene of both feet seventeen days after the onset of a scarlet fever rash. Tight swelling of the feet and lower legs immediately preceded the gangrene and was believed to have caused the gangrene by pressure. Both feet were icy cold. A large bruise on the left thigh, a bleeding time of seven minutes, and a platelet count of 36,000 was taken as evidence that purpura may have been the cause of the swellings. Both limbs were amputated just below the knees nearly three weeks after the onset of gangrene, with no trial of incision for relief of pressure. Reexamined a year after his illness he was well and free from further purpura.

MONTGOMERY.

Lambie, G. G., and Morson, S. M.: Acrocyanosis. *M. J. Australia* 2: 1070, 1937.

A single case of acrocyanosis is presented in detail. Arms, legs, and cheeks were especially involved. This case is unusual in that it is of a young woman with

disturbances of bodily growth, metabolism, and mental development. Also, seven close relations had chilblains of the extremities. The patient's symptoms were coldness and blueness of the extremities, aggravated by cold weather, chilblains of the fingers which had ulcerated, and of the toes which had not. Considerable relief was obtained by proper protection from cold.

X-ray revealed no evidence of calcification of arteries. Heating the patient produced a skin temperature rise to the level found in normal people so treated. When blood flow through a limb was interrupted by means of a blood pressure cuff, and the part warmed, and pressure released (reactive hyperemia, Pickering test), the resultant flush occurred nearly as fast as it does in a normal person. Nerve block (ulnar) abolished the abnormal vessel reactions, over the area of nerve distribution.

The differentiation of acrocyanosis from Raynaud's phenomena was made by the following findings: the abnormality was constant (nonparoxysmal), there was no blanching or pain, and all evidence pointed to the fact that only the most distal vessels (arterioles) were affected.

MONTGOMERY.

Neurath, O.: The Determination of Circulation Time With Magnesium Sulfate. *Ztschr. f. Klin. Med.* 132: 134, 1937.

The author uses 5 c.c. of 10 per cent solution of magnesium sulfate, which leads to a sudden sensation of warmth in the head. No side reactions were noted. The method of determining circulation time is the standard one. He found circulation times of 11 to 17 seconds in normal persons, 12 to 26 seconds in persons with hypertension without heart failure, and 13 to 58 seconds in persons with hypertension with heart failure. In thyroid disease the circulation time is accelerated. This is also true in paroxysmal tachycardia, except when the heart rate is above the critical value when the circulation time is prolonged. No difference was found between "right and left heart failure."

KATZ.

Heckmann, K.: The Changes in the Heart's Position During Its Pulsation and Its Appearance in the Roentgenkymogram. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 55: 319, 1937.

Many of the waves in the roentgenkymogram are due to position changes in the heart. This study is based on a comparison of types of curves obtained in man with those in model experiments; and also on observations of movements of a case with pericarditis calculosa. Double waves are to be explained as due to a combination of actual pulsations and changes in the heart's position.

KATZ.

Heckmann, K.: Pulsations in the Pulmonary Vessels and Their Manifestations in the Kymogram. *Klin. Wchnschr.* 16: 733, 1937.

Pulsations in the region of the pulmonary artery are caused not only by this vessel, but also by the aorta. In congestion of the lesser circuit, the author finds the trapeze form in the roentgenkymogram, indicating an increased resistance to flow peripherally from the pulmonary artery; hence the decrease in the pulse occurs later in diastole. Double waves are due to interference between pulmonary and aortic pulsations when the two pulses are noticeably asynchronous. The splintering of the pulmonary wave occurs also in open ductus Botalli. This last is attributed to asynchrony of the pulses transmitted from the right ventricle and through the ductus.

KATZ.

Book Review

ARTERIOVENOUS ANEURYSM. Abnormal Communications Between the Arterial and Venous Circulations. By Emile Holman, A.B., B.A. Oxon., M.D. Professor of Surgery, Stanford University Medical School; Surgeon-in-Chief, Lane and Stanford University Hospitals. New York, 1937, The Macmillan Company, Price \$5.00.

The experimental arteriovenous fistula as produced by the author is described, and this is followed by a careful study of the local manifestations as well as the effects produced upon the remainder of the circulatory system. The physiologic effects upon the circulation following the establishment of a fistula that are considered include: Fall in the blood pressure, increased cardiac contraction, increased total blood volume, and increased cardiac output. The reversal of the condition, viz., closure of the fistula, causes the blood pressure to rise again and decreases the cardiac contraction, the total blood volume, and the cardiac output. The experimental data are compared with the clinical observations. In his discussion the author has properly pointed out the effect of the fistula upon the heart, the increased surface temperature beyond the fistula, and the increase in the size of the extremity in the presence of a fistula.

Efficiently presented are the clinical examples of arteriovenous fistula, including the acquired intracranial arteriovenous aneurysms, intrathoracic arteriovenous communications, mycotic arteriovenous aneurysms, and the congenital arteriovenous communications of the peripheral vessels. The physiologic changes due to open ductus arteriosus have been elaborated upon following the experimental production of interventricular septum defects.

The physiologic problems are of fundamental importance and may be far-reaching. Study of these fundamental principles may bring forth an explanation of the development of cardiovascular disease and hypertension. Although arteriovenous communications may be rare, as has been pointed out by the author, they afford an excellent opportunity for increasing our knowledge of the physiology of the mechanisms that control the circulation.

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Original Communications

CLINICAL STUDIES OF GITALIN AND OF DIGITALIS IN THE TREATMENT OF AURICULAR FIBRILLATION*

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THE present study was undertaken to compare clinically the actions of digitalis leaf and gitalin.† In 1912 Kraft¹ obtained a new substance from a cold water extract of digitalis leaves. The drug which he called gitalin was subsequently introduced under the name of verodigen. Gitalin (amorphous) is a glucosidal fraction of *Digitalis purpurea* which is extracted from a cold water infusion by means of chloroform after the removal of saponins and digitalic acids with basic lead acetate. The chloroform extract is concentrated *in vacuo* and the amorphous gitalin precipitated with petroleum ether, and subsequently dried without heat to constant weight. It occurs as a yellowish-white amorphous powder which is very soluble in chloroform and alcohol, and in about 800 parts of cold water. In the dry state gitalin (amorphous) is stable, as shown by biologic assays over periods of years. The potency is apparently quite uniform and the minimum lethal dose by the Hatcher-Brody cat method² is approximately 0.8 mg. per kilogram.³ Straub⁴ found from his pharmacologic studies that gitalin possesses all the properties common to the digitalis bodies. The more important European communications dealing with the actions of gitalin are reviewed by Mansfeld and Horn.⁵ The clinical potency of gitalin and of other digitalis bodies does not always correspond to the biologically determined potency; hence reports in the literature are conflicting. The European studies (both pharmacologic and clinical) indicate that 0.8 mg. ($\frac{1}{80}$ grain) of gitalin is equivalent to 0.1 gram of digitalis leaf.^{4, 5} Stroud found that the quantity of gitalin representing one cat unit biologically (0.8 mg.) did the work clinically of 3 cat units (0.3 gm.) of digitalis. Our own studies show that the biological cat unit of gitalin (0.8 mg.) is equivalent clinically

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†The drugs used in this study were supplied by the Rare Chemical Company, Nepera Park, New York.

to 2 cat units of digitalis (0.2 gm.). In a recent study⁶ of urginin, a squill glucoside, a discrepancy between clinical and biologic units of the drug was also found; approximately 2 cat units of urginin were required to obtain the same clinical effects as 1 cat unit of digitalis.

MATERIAL

Thirty-six ambulant patients with auricular fibrillation were observed at our office for periods of six to thirteen months. Each patient was seen from fifteen to twenty times during the study. There were twenty-one women, the majority of whom were housewives, and fifteen men, nearly all of whom were workers at occupations calling for slight to moderate exertion. Twenty-eight patients (78 per cent) had chronic rheumatic valvular disease; one (3 per cent) had had a coronary thrombosis; and one (3 per cent) had hyperthyroidism. The remaining six patients (16 per cent), all men, had no evidence of valvular disease, coronary arteriosclerosis, hyperthyroidism, or previous hypertension. The cause of their cardiac irregularity is unknown. For the entire group, the average age at the onset of auricular fibrillation was 41.6 years. Auricular fibrillation had existed, on the average, for 2.6 years prior to the beginning of the study. This figure was greatly lowered by the fact that several patients presented themselves for the first time at the onset of their irregularity. There were eight patients in whom auricular fibrillation had lasted four or more years; one, seven years; and one, nine years. The longest period of auricular fibrillation occurred in a man aged 64 years, in whom it had commenced twenty-one years previously, at the age of 43 years. In him the auricular fibrillation is of unknown etiology.

At the time of the study, the average age of the patients was 44.2 years. In twenty-eight of the thirty-six patients the blood pressure was normal; in eight there was some degree of hypertension, ranging from 150 systolic to a maximum of 190 systolic. The left auricle was enlarged in all cases except one, as determined by fluoroscopy; the enlargement was moderate in nine cases, marked in nineteen cases, and extreme in seven cases.

During the study there was only one death. Progressive dyspnea, cough, frank hemoptysis, irregular fever, basal pulmonary signs, and increasing scleral icterus suggested that reactivation of the rheumatic process was the immediate cause of this patient's progressive heart failure and death. It is of some interest that he was the only patient whose subjective symptoms, including his cough, which was at times productive of blood, were out of proportion to his physical findings. These symptoms, very likely due to reinfection, were present for months before the more acute terminal illness. The rôle of reinfection in persons dying with rheumatic heart disease has been stressed in recent years.⁷

In twenty-seven patients the maintenance doses of both gitalin and of digitalis were established. By "maintenance dose," we mean the smallest amount which would keep the patient comfortable and maintain his ventricular rate at approximately 68 to 88 beats per minute. Each drug was administered long enough to be sure that the minimal dose was constant. Due consideration was given to the discrepancy between the maximum and the minimum digitalis dosage necessary for clinical maintenance.⁸ The heart rates were counted either by stethoscope or from electrocardiographic tracings after the patients had been resting on the examining table for at least one minute, and after a preliminary rest period in the waiting room for at least ten minutes. Gitalin was given first in each case. It was dispensed in tablets of 1/80 grain, scored into three equal parts. After the maintenance dose had been ascertained, which usually required several weeks, the gitalin

was replaced by a standard preparation of digitalis (dried leaves, each tablet containing $1\frac{1}{2}$ grains, i.e., 1 cat unit). The dose of digitalis was then adjusted over a period of several weeks until approximately the same heart rate was obtained.

RESULTS

The results are summarized in Table I, which shows that the daily maintenance dose of digitalis was $\frac{1}{2}$ cat unit in two patients, 1 cat unit in ten patients, $1\frac{1}{2}$ cat units in six patients, 2 cat units in eight patients, and 3 cat units in two patients. The average for the group of twenty-eight patients to whom the drug was given was $1\frac{1}{2}$ cat units ($2\frac{1}{4}$ grains).

TABLE I

COMPARISON OF MAINTENANCE DOSAGE OF DIGITALIS AND OF GITALIN

CASES		GITALIN—		DIGITALIS—	
		DAILY DOSE IN GRAINS	AVERAGE APICAL RATE	DAILY DOSE IN CAT UNITS	AVERAGE APICAL RATE
1.	R. A.	$\frac{1}{120}$	78	$1\frac{1}{2}$	70
2.	J. B.	$\frac{1}{240}$	64	$\frac{1}{2}$	72
3.	M. B.	$\frac{1}{80}$	88	$1\frac{1}{2}$	86
4.	N. B.	$\frac{1}{240}$	72	1	74
5.	V. C.	$\frac{1}{120}$	86	1	88
6.	I. C.	$\frac{1}{80}$	86	3	88
7.	J. F.	$\frac{1}{240}$	72	$\frac{1}{2}$	68
8.	A. F.	$\frac{1}{120}$	72	$1\frac{1}{2}$	68
9.	I. G.	$\frac{1}{240}$	74	1	70
10.	D. G.	$\frac{1}{160}$	72	$1\frac{1}{2}$	76
11.	J. G.	$\frac{1}{240}$	82	1	74
12.	G. G.	$\frac{1}{100}$	86	$1\frac{1}{2}$	88
13.	F. G.	$\frac{1}{240}$	78	1	76
14.	H. I.	$\frac{1}{80}$	86	2	80
15.	L. K.	$\frac{1}{100}$	80	2	80
16.	R. K.	$\frac{1}{80}$	84	2	86
17.	I. K.	$\frac{1}{80}$	80	2	70
18.	H. L.	$\frac{1}{160}$	72	1	74
19.	S. P.	$\frac{1}{120}$	78	1	80
20.	S. P.	$\frac{1}{80}$	88	1	86
21.	G. R.	$\frac{1}{100}$	82	2	80
22.	K. S.	$\frac{1}{40}$	84	2	82
23.	D. S.	$\frac{1}{80}$	76	2	72
24.	L. S.	$\frac{1}{50}$	84	2	86
25.	R. S.	$\frac{1}{80}$	82	3	84
26.	S. W.	$\frac{1}{120}$	72	$1\frac{1}{2}$	72
27.	Y. W.	$\frac{1}{80}$	88	1	84
Average		$\frac{1}{110}$		$1\frac{1}{2}$	

The daily maintenance dose of gitalin was found to be $\frac{1}{240}$ grain in six patients; $\frac{1}{160}$ grain in four patients, $\frac{1}{120}$ grain in nine patients, $\frac{1}{100}$ grain in four patients, $\frac{1}{80}$ grain in nine patients; $\frac{1}{50}$ grain in one patient, and $\frac{1}{40}$ grain in one patient. The average for the group of thirty-four patients to whom gitalin was administered was $\frac{1}{110}$ grain. From a comparison of these maintenance doses of the two drugs, one may conclude that, clinically, $\frac{1}{160}$ grain of gitalin is equivalent to 1 cat unit of digitalis. This is at variance with the observations of

Stroud and his associates,³ who found that $\frac{1}{240}$ grain of gitalin was the clinical equivalent of 1 cat unit of digitalis (approximately $1\frac{1}{2}$ grains of the powdered leaves).

Table I shows that $\frac{1}{160}$ grain of gitalin and 1 cat unit of digitalis are not equivalent in every case (e.g., cases 6, 20, 22, 24, 25), but in any given case the ratio between the maintenance doses of the two drugs remains constant. We determined this by giving a patient first one drug, then the other, and then the first one again. We are unable at present to explain the variation in the equivalent doses of the two drugs. It may depend on differences in absorption, elimination, and duration of action. Patients in whom the equivalent doses departed markedly from the average exhibited some degree of heart failure during this whole study.

An additional complicating factor is the well-known fact that the digitalis requirements of different patients vary considerably, irrespective of the particular form of digitalis that is prescribed. In the present series of cases we reviewed the following factors in relationship to digitalis dosage: The size of the left auricle, the size of the left ventricle, previous attacks of heart failure, the degree of neuro-circulatory imbalance, degree of heart failure present, and body weight. The cases are too few in number to allow of statistical deductions, but, as far as the figures go, no relationship between any of these factors and the size of the digitalis dose can be demonstrated. The only possible exception is that seven patients who weighed 160 lb. or more all required doses of digitalis larger than the average.

Of the twenty-nine patients who gave a statement relative to preference for either gitalin or digitalis, sixteen had no preference, six preferred gitalin, and seven preferred digitalis. The reasons for preference were not significant; some felt less tired, less dizzy, or less choked, on one or the other drug.

There was close correspondence between gitalin and digitalis in their effect upon the R-T segment and T-wave of the electrocardiogram. In eleven patients neither drug in therapeutic doses produced T-wave changes. In twelve patients both drugs produced slight T-wave changes, in ten patients moderate changes, and in two patients marked changes. There were insignificant discrepancies in only two patients.

Eight patients were studied in an attempt to compare the persistence of action of the two drugs. The heart rate was used as a measure of persistent digitalis effect. Gitalin was discontinued until the heart rate rose to 120 beats per minute or until the prior appearance of increased dyspnea, fatigability, distressing palpitation, or weight gain. Then digitalis was given, and, when the rate was again controlled, digitalis was withdrawn. The cases are too few and the results too variable to allow of categorical conclusions, but it is clear

that the gitalin effect lasted at least as long as digitalis, if not a bit longer. Haag,⁹ working with pigeons, found persistence of action of five to ten days with tinctures of digitalis, and of about two weeks with gitalin.

Eight patients when first seen had been taking no digitalis and had rapid ventricular rates. The average rate was 138 beats per minute at the time of examination. These patients were given large doses of gitalin within a few days (average $2\frac{1}{2}$ days). At the end of this period the average ventricular rate was 84 beats per minute. The average amount of gitalin that effected this slowing was $\frac{7}{80}$ grain. This, according to our other studies, is equivalent to 14 cat units of digitalis. This corresponds to general clinical experience with digitalis dosage¹⁰ and also agrees with the observation by Stroud and his associates³ that clinical improvement and slowing of the ventricular rate in untreated patients with auricular fibrillation are effected by a total dosage of $\frac{1}{16}$ to $\frac{1}{10}$ grain of gitalin. Baker and Bloom¹¹ also found that the quantity necessary for complete digitalization varies from $\frac{6}{80}$ to $\frac{10}{80}$ grain. Our results with rapid digitalization give further evidence that $\frac{1}{160}$ grain of gitalin is equivalent clinically to 1 cat unit of digitalis.

Luten¹² has recently claimed that in patients with auricular fibrillation without heart failure therapeutic doses of digitalis produce no slowing of the ventricular rate. This statement is at variance with our experience. We studied several patients who had been taking no digitalis and showed no clinical evidence of heart failure. In all of these cases the range of the ventricular rate was reduced rapidly from 118-160 beats per minute to 76-100 beats per minute by gitalin medication.

CASE 1.—E. F., a woman 46 years of age, with mitral stenosis, mitral insufficiency, and aortic insufficiency, had had auricular fibrillation for less than a year. She had not taken digitalis during the two weeks immediately preceding her office visit. On examination the lungs were clear, the liver was not enlarged, and there was no peripheral edema. The ventricular rate was 140 beats per minute. Fluoroscopic examination showed that there was moderate enlargement of the chambers of the heart. Within twenty-four hours she was given seven tablets (each $\frac{1}{80}$ grain) of gitalin, and the ventricular rate was slowed to 76 beats per minute. There was no subsequent weight loss.

CASE 2.—N. B., a man 39 years of age, gave no history of rheumatic fever, but had known that he had a heart murmur for about twenty years. During these twenty years, he had experienced occasionally, and more frequently during the year immediately preceding, sudden attacks of palpitation and irregularity of the heart beat, lasting about forty-eight hours and ending abruptly. He had taken no digitalis for ten years, and had never taken any quinidine. He was examined the day after his last attack of palpitation. There was slight cyanosis of the lips. The lungs were clear. The liver was not enlarged. Fluoroscopically there was great enlargement of the left auricle and right ventricle and slight enlargement of the left ventricle. The first heart sound was sharp and was preceded by a diastolic

rumble. There was a diastolic murmur to the left of the sternum. The heart-beat was absolutely irregular, and the rate was 136 beats per minute. The blood pressure was 120/90. Within three days 1/10 grain of gitalin was given and the heart rate dropped from 140 to 76 beats per minute. The dose of gitalin was sharply reduced, but four days later the rate had dropped to 48 beats per minute. Except for the slowed apical rate there was absolutely no change in his physical findings, and no loss in weight occurred.

CASE 3.—M. B., male. At the age of 36 years, auricular fibrillation was discovered. There was no history of rheumatic fever or of a murmur. At the age of 39 years, when he was first examined at the office, the lungs were clear, and fluoroscopically there was considerable enlargement of the left ventricle. The heart sounds were of good quality. There were no murmurs. Auricular fibrillation was present, and the ventricular rate was 80 per minute. (He had been taking some digitalis in the preceding few days.) The blood pressure was 138/100. During the next five years he worked steadily as a painter. There was slight dyspnea on walking seven blocks. He continued to take small amounts of digitalis irregularly. When examined again, at the age of 44 years, the lungs were clear and the liver was not enlarged. Fluoroscopically there was considerable enlargement of the left ventricle and moderate enlargement of the left auricle. The first heart sound was of good quality. There were no murmurs. The apical rate varied from 84 to 100 beats per minute. The blood pressure was 125/100. He was given gitalin, and his heart rate was maintained between 80 and 90 on 1/80 grain daily. The drug was then withdrawn for twenty-four days. At the end of this time the apical rate had risen to 112 beats per minute, and he noted some increase in dyspnea on climbing stairs. On a standard exercise tolerance test his apical rate increased from 112 to 122 beats per minute. The circulation time (when the heart rate was 112 per minute) was 17.5 sec. by the decholin method.¹³ To physical examination his condition was unchanged. The lungs were clear, the liver was not enlarged, there was no peripheral edema, and there had been no increase in weight. He was then given 2 cat units of digitalis a day for one week. At the end of this period his heart rate was 74 beats per minute. His condition was still unchanged, and there had been no weight loss.

CASE 4.—One of us¹⁴ reported in a previous communication the case of a woman, 50 years of age, with Graves' disease of two years' duration. There was sweating, tremor of the hands, and progressive weight loss. Irradiation of the thyroid gland by means of radium had been ineffectual. There was considerable enlargement of the left ventricle, and auricular fibrillation was present. The basal metabolic rate was + 65 per cent. The heart rate was recorded by means of the cardiometer both before and after digitalization (the patient received 61 c.c. of the tincture of digitalis in sixteen days). The resting rate before digitalis was given was approximately 116 beats a minute, as compared with 98 per minute after digitalization. There had been no subjective or objective evidence of heart failure before digitalization.

When gitalin was withdrawn from several of the patients the ventricular rates rose from approximately 80 to an average of 112 beats per minute; no clinical evidence of heart failure was found at these high rates. When digitalis was then administered, the rates were again slowed to the same degree. Of eight cases, in which withdrawal of one or the other drug caused increases in ventricular rate without concomitant clinical evidences of heart failure, the circulation

time was measured in six, both before and after digitalization, using the decholin method. The results are shown in Table II. In none of these six cases was there any significant change in the circulation time when the ventricular rate was rapid and the patient was not under the influence of digitalis. Observation both of untreated patients and of those from whom the drug could be withdrawn at will indicates that, in many cases at least, the increased ventricular rate is not due to heart failure and that it can be readily slowed by appropriate doses of digitalis. These clinical studies do not substantiate Luten's contention that slowing by digitalis of the ventricular rate in auricular fibrillation is effected only when heart failure is present.

It seems logical at this point to question the value of slowing the ventricular rate if no heart failure ensues because of the rapid rate. However, patients feel much better with slower rates, notice less palpitation on slight or moderate exertion, and do not experience the throbbing and violent palpitation on exertion or emotion that occur in those with uncontrolled auricular fibrillation. Even at rest the uncontrolled rapid rate is distressing and makes patients more heart-conscious.

TABLE II

CIRCULATION TIME STUDIES IN PATIENTS, DIGITALIZED AND UNDIGITALIZED

PATIENT	DIGITALIZED		UNDIGITALIZED	
	CIRCULATION RATE IN SECONDS	APICAL RATE	CIRCULATION RATE IN SECONDS	APICAL RATE
R. A.	18.5	66	17.5	106
I. G.	16.5	60	15.5	72
S. P.	15.0	80	14.0	88
F. G.	21.0	86	22.0	106
I. K.	13.5	72	15.0	90
H. L.	18.0	72	19.0	100

H. I., male, gave no history of rheumatic fever, but at the age of 45 years his application for life insurance had been rejected because of a murmur. At the age of 50 he had had an attack of palpitation with rapid heart rate, lasting three days. When he was examined a week after this attack, auricular fibrillation was present, and the ventricular rate was 160 beats per minute. There was extreme enlargement of the left auricle and both ventricles. The blood pressure was 125/100. The lungs were clear and the liver not enlarged. Unusually large doses of gitalin, administered over a period of weeks, were required to reduce his heart rate to a range of 72 to 84 beats per minute. He had been afebrile. His basal metabolic rate was -15 per cent. The sedimentation time of the red blood cells was over one hour for 18 mm. Once controlled, he was maintained adequately on 1/80 grain of gitalin, and subsequently on 2 cat units of digitalis. When he was digitalized, he experienced no racing of the heart on exertion. He was able to walk considerably more, and stair climbing induced less dyspnea; yet he exhibited no manifest heart failure when his ventricular rate was rapid.

In patients with auricular fibrillation but without heart failure the uncontrolled rapid irregular rate acts as a mechanical embarrassment

to an already damaged heart. Rapid rates, regular or irregular, may produce no symptoms when the myocardium is normal, but persistent rapid rates are injurious to diseased hearts. Enlarged hearts, in particular, are more likely to fail when their beating is persistently rapid.¹⁵ Even in patients with auricular fibrillation whose ventricular rates are relatively slow when they are at rest, it is best to administer small doses of digitalis, because exertion then provokes less discomfort, palpitation, and acceleration of the heart rate.

TOXIC REACTIONS

Overdosage with gitalin produces toxic effects similar to those produced by overdosage with whole leaf digitalis preparations.³ Toxic reactions and untoward effects during digitalis administration are singularly few when the drug is used with care. On only a very few occasions in the present study were mild toxic symptoms encountered with either drug—nausea in a few patients and extrasystoles in two patients. Even in the group in which large doses of gitalin were administered to effect rapid slowing of the ventricular rate, no toxic symptoms were encountered. In using either drug, one must constantly keep in mind the great individual variations in maintenance dosage, and ascertain by experiment the proper amount for each patient. Dosage according to body weight serves as a rough guide in treating the acutely ill, but it is unreliable when the drug must be given for long periods of time. On very rare occasions, digitalis cannot be taken by mouth. Rectal administration is often efficacious in such cases. Digitalis products may be dispensed in colored capsules for patients who have developed an aversion to the use of green digitalis tablets. In such cases, too, the administration of a white digitalis preparation, such as gitalin, is equally effective.

SUMMARY

A comparative study of the actions of gitalin and digitalis was made in thirty-six ambulant patients with auricular fibrillation.

Gitalin acts like digitalis in slowing the ventricular rate and relieving congestive heart failure in patients with auricular fibrillation.

Gitalin parallels digitalis in its effect on the R-T transition and T-waves of the electrocardiogram.

Gitalin has a persistence of action at least as long as digitalis.

Rapid administration of gitalin in eight patients produced prompt and effective slowing of ventricular rates and clinical improvement without the development of toxic symptoms.

The average daily maintenance dose of gitalin was $\frac{1}{110}$ grain; of digitalis, $2\frac{1}{4}$ grains, or $1\frac{1}{2}$ cat units.

Clinically, $\frac{1}{160}$ grain of gitalin is equivalent to 1 cat unit of digitalis leaves.

The daily maintenance dosages of both drugs show considerable variations in different individuals.

Toxic reactions to gitalin are the same as to digitalis. They are neither more nor less frequent. With careful administration they should be rare with either drug.

Our studies indicate that digitalis can slow ventricular rates in auricular fibrillation in the absence of heart failure, which is contrary to the contention that slowing of the ventricular rate in auricular fibrillation is effected by digitalis only in the presence of heart failure.

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ANGINA PECTORIS AND MYOCARDIAL INFARCTION AS COMPLICATIONS OF MYXEDEMA

WITH ESPECIAL REFERENCE TO THE DANGER OF TREATMENT WITH
THYROID PREPARATIONS^{*}

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MYXEDEMA complicated by angina pectoris has been observed frequently, but a fatal outcome resulting from myocardial infarction during treatment with thyroid is rare. As far as could be determined only eight such cases have been reported, and in only five of these was the diagnosis confirmed at autopsy. The purpose of this communication is to review these previously reported cases and to record one additional case.

Numerous observers (Christian,¹ Sturgis,² Sturgis and Whiting,² Fahr,⁴ Abrami and co-workers,⁵ and Gordon⁷) have warned of the dangers encountered in the use of desiccated thyroid gland in the treatment of patients with myxedema, especially when cardiac symptoms are present. Because of the widespread use of this substance in mild hypothyroid states and the recent production of artificial myxedema as a mode of treatment in myocardial failure and angina pectoris (Blumgart, Levine, and Berlin⁶), it seems timely to re-emphasize the need for caution in the administration of this drug and to stress the importance of watching for signs of cardiac failure when it is used.

REVIEW OF THE LITERATURE

The occurrence of cardiac pain in myxedema was first reported by Hertoghe,⁹ in 1914; he attributed it to a myxedematous change in the nerve cells of the connective tissue of the heart. Zondek,¹⁰ who introduced the term "myxedema heart," mentioned pain in myxedema but gave no details concerning its type or distribution. In 1924, Laubry, Mussio-Fournier and Walser¹¹ reported the first case of true angina pectoris associated with myxedema. They thought that arteriosclerosis played a part in the production of the pain but that it was largely "functional" in origin. The first American account of this complication was published by Christian¹ in July, 1925. The patient was a woman, 50 years of age, with severe constricting pain in the chest, of one year's duration, which had the typical radiation of angina pectoris. The basal metabolic rate was -32 per cent. After taking 0.52 gm. of thyroid daily for four days she developed circulatory failure. There was temporary

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recovery following reduction of the dose to 0.13 gm. daily, but later she went into shock and died of coronary occlusion sixteen days after the treatment was instituted. This case is particularly interesting because it closely parallels the one reported herein.

Fahr,¹² who reported the first cases of myxedema heart in this country, found one man, 49 years of age, who had occasional attacks of precordial pain on exertion. This symptom disappeared after five months' treatment with desiccated thyroid. Since that time other observers have noted the improvement or disappearance of angina following thyroid therapy (Chapman,¹³ Higgins,¹⁴ Ziskin¹⁵). Gordon,⁷ on the other hand, had one patient, a woman 62 years of age, who developed angina following the injection of 10 mg. of thyroxin. He also observed a man who developed precordial pain which radiated down both arms while under treatment for hypothyroidism with 0.32 gm. of desiccated thyroid gland daily.

The difficulty of treating a patient who has both myxedema and heart disease has frequently been observed. Escimilla¹⁶ reports a case of myxedema illustrating this problem. The patient had had chest pain for three years. A dose of 0.065 gm. of desiccated thyroid was not tolerated because of angina, and therefore the dose was gradually reduced to 0.015 gm. once per week, but even with this small amount some localized pain over the heart continued.

Little attention has been paid to the association of angina or myocardial infarction with myxedema. In 1925, Willius and Haines,¹⁷ in a report of 162 cases of high-grade myxedema, observed only one patient with angina. The following year, Means, White, and Krantz,¹⁸ in reviewing 48 cases of myxedema, found one patient who developed twinges of pain following the use of thyroid in doses of 0.12 gm. per day. One of Lerman, Means and Clark's¹⁹ 18 patients with myxedema suffered from angina before thyroid medication was started and died at home, probably of coronary occlusion. In the following series of cases of myxedema there is no mention of cardiac disease: Case²⁰ (58 cases), Lawrence and Rowe²¹ (120 cases), Riecker²² (64 cases). All accounts of either angina pectoris or coronary occlusion complicating myxedema are isolated instances and so give no indication of the incidence of this combination of diseases.

Wegelin²³ and Ohler and Abramson²⁴ have called attention to the fact that little autopsy material is available for the study of myxedema. The following are summaries of all of the cases of myxedema and myocardial infarction due to coronary occlusion in the American literature.

CASE 1.—Christian,¹ in 1925, and Sturgis and Whiting,³ in 1926, reported a case of myxedema and angina pectoris in a woman 50 years old. Her treatment consisted of 0.13 gm. of dried thyroid gland three times a day for two days, then 0.13 gm. four times a day for two days. The drug was discontinued when she developed cyanosis, a feeble pulse, and other signs of acute cardiac failure. Recovery fol-

lowed, and on the sixteenth hospital day treatment was resumed with 0.03 gm. of thyroid three times a day, but death occurred forty-eight hours later. Autopsy showed coronary atherosclerosis, cardiac infarction, hypertrophy and dilatation of the heart, atrophy and fibrosis of the thyroid gland, and generalized atherosclerosis.

CASE 2.—Fahr,⁴ in 1932, reported a case in a woman aged 46 years who gave a history of hoarseness, slowness of speech, sluggishness, loss of memory, depression, dryness of the skin, and coldness of the hands and feet, all of two years' duration. She had had several attacks of severe precordial pain which usually came on after exertion and was relieved by rest. The basal metabolic rate was -25 per cent. She was advised to take 0.065 gm. of thyroid extract twice a day. Six days later she returned extremely nervous and apprehensive, saying that she had taken very little of the drug. She had experienced one attack of angina which was not relieved by morphine. In the hospital she received 0.13 gm. of desiccated thyroid daily. Another attack occurred on the eleventh hospital day, and thereafter, until her death three months later, angina occurred every day. Autopsy was limited to the heart, which weighed 475 gm. and showed almost complete occlusion of the left descending branch of the coronary artery with a fresh thrombus in its lumen. The other two branches were narrowed. There was necrosis of the heart muscle, indicating that the accident must have occurred a few days before death.

CASE 3.—Means and Lerman,²⁵ in 1935, gave an account of a housewife, 52 years of age, who for two or three years prior to entry had slowly been developing symptoms characteristic of myxedema. Her basal metabolic rate was reported to be low. Thyroid was taken in full doses (0.3 gm. tablets, one and one-half tablets the first day, two tablets the second day, two and one-half the third day, and three tablets per day thereafter), whereupon she developed massive edema of the extremities, swelling of the abdomen, marked dyspnea and orthopnea, and some precordial aching. Both she and her doctor were sure that the thyroid produced these symptoms, and it was therefore discontinued. On admission, examination revealed signs of myxedema and cardiac failure. The basal metabolic rate was normal because of the thyroid that she had received. It was thought that she had heart disease, probably rheumatic, with mitral regurgitation. On full doses of digitalis the cardiac symptoms improved, and the basal metabolic rate fell to -32 per cent. She was discharged, and returned four months later with fully developed myxedema but no signs of decompensation. Thyroid was administered in doses of 0.032 gm.; it was well tolerated and relieved the myxedematous manifestations. The third admission was because of recurrence of the dropsy. The patient died very suddenly. Autopsy showed that the thyroid was atrophic. The heart weighed 600 gm. The right ventricle was dilated and hypertrophied. The changes in the mitral valve were such as to produce regurgitation but not stenosis. Both coronary arteries showed lesions. In the left there were calcification and fibrosis; the lumen was reduced to about one-half of its normal caliber and at one point was narrowed still further by a fresh red thrombus. The right coronary showed narrowing and thickening but no calcification. It was thought that the immediate cause of death was a fresh coronary occlusion and that the myxedema, by diminishing the work of the heart, probably postponed death rather than hastened it.

CASE 4.—Higgins,¹¹ in 1936, reported a case in a woman, 52 years of age, who was admitted complaining of weakness. She was mentally sluggish and had a dry skin. The basal metabolic rate was -26 per cent. There was complete remission of symptoms after thyroid therapy. Her last illness followed a two months' interruption of treatment. She entered with signs of cardiac failure. Improvement followed treatment with thyroid, but while still in bed she developed precordial pain which was followed later by symptoms of coronary occlusion. Autopsy showed that the heart

was somewhat hypertrophied, that all of the coronaries were much thickened, and that the left ventricular wall was very thin and composed of fibrous tissue. Microscopically the myocardial changes were such as are commonly found in patients with coronary atherosclerosis.

CASE 5.—In the same paper Higgins¹⁴ gives an account of a woman, 55 years of age, who complained of weakness and swelling of the extremities. With the exception of the basal metabolic rate, which was -33 per cent, the examination was negative. Her symptoms disappeared under thyroid therapy. Four months before her second admission to the hospital she suffered an attack typical of coronary occlusion, from which she made a slow but satisfactory recovery. The symptoms at the time of her second admission were dyspnea, swelling of the legs, and weakness. Examination revealed enlargement of the liver, which extended a hand's breadth below the costal border, and signs of fluid at the bases of both lungs. Her death was apparently caused by progressive coronary disease. Autopsy revealed extremely sclerotic coronaries, with reduction of their lumina to pin-point size. The apical half of the left ventricular myocardium was almost completely replaced by fibrous tissue, which was about one-eighth of an inch thick at the apex.

In addition to these five cases of myxedema and myocardial infarction in which autopsies were performed, clinical reports of three cases of myxedema in which sudden death followed thyroid therapy have been published.

Graves,²⁶ in 1927, treated a woman 54 years of age who had symptoms of myxedema and a basal metabolic rate of -40 per cent. After taking 1 gm. of desiccated thyroid daily for three days she developed symptoms of coronary occlusion and died. Lerman, Means, and Clark¹⁹ observed a man, 55 years of age, with angina pectoris and a basal metabolic rate of -29 per cent. The electrocardiogram showed bundle branch block. Although the authors made no statement regarding therapy, it may be assumed that the patient was treated with thyroid. A year later he died suddenly at home, probably of coronary occlusion. Ohler and Abramson's case²⁴ was that of a man, 30 years of age, who had a basal metabolic rate of -21 per cent and edema of the lower extremities. He received 0.972 gm. of desiccated thyroid daily, and the edema disappeared; but four days after he was discharged from the hospital, he suddenly complained of severe pain in the left shoulder, dropped to the floor, and died half an hour later. The authors were of the opinion that his death was due to coronary occlusion, and that the latter was at least partly the result of excessive doses of thyroid.

The following is an additional case of myxedema and angina pectoris. The patient died of myocardial infarction on the eighth day of treatment with desiccated thyroid.

REPORT OF CASE

History.—L. C., a woman 63 years of age, was admitted to the Medical Service of the University of Michigan Hospital March 8, 1937, complaining of fatigability, listlessness, and pain in the upper right quadrant of the abdomen and around the heart. The abdominal pain had been periodic and colicky, and radiated along the right costal margin to the right scapula. Jaundice had been noted with some of the attacks. Five years earlier she had begun to notice that she was becoming sluggish and was articulating with difficulty and that her hair seemed dry, her voice husky

and her face and eyelids puffy. At that time she was told that she would have to take thyroid the remainder of her life. Treatment helped her, but she had taken no thyroid for two years prior to admission, and not only had all of her original symptoms returned, but, in addition, she had developed retrosternal pain, attended with a sense of weight on the chest, which was brought on by exertion and at times radiated down both arms. Rest and nitroglycerin had given immediate relief.

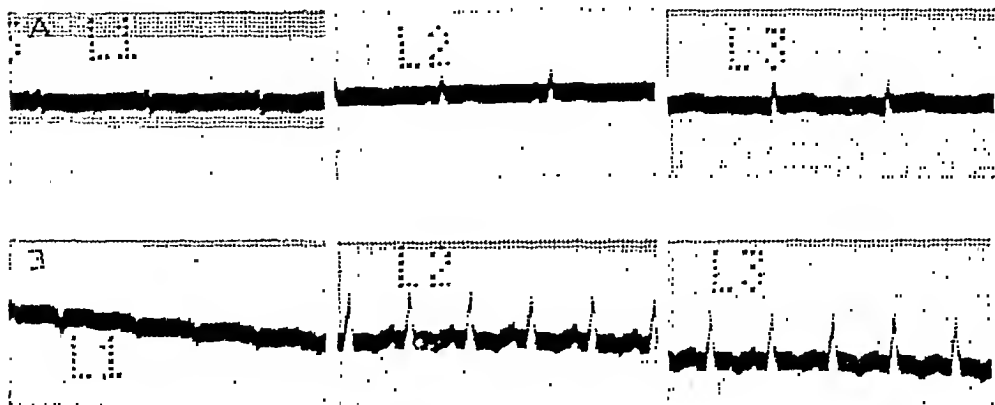


Fig. 1.—A, before treatment. B, day of death.

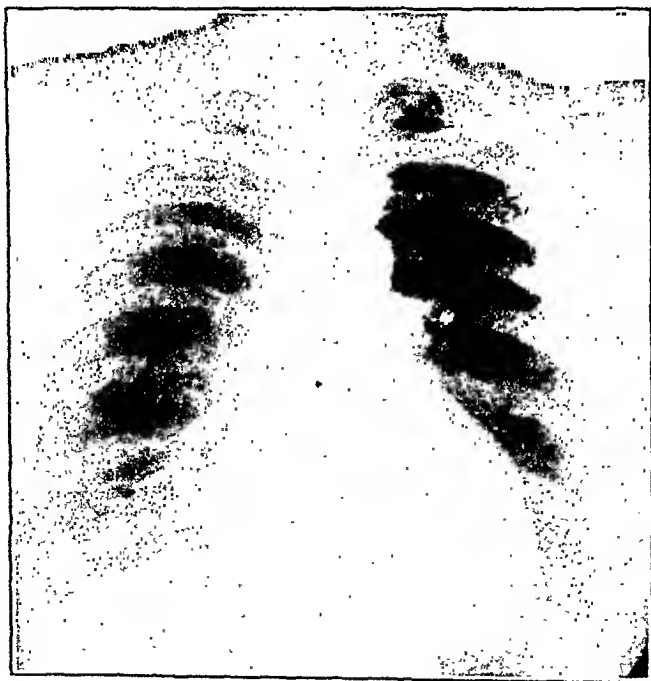


Fig. 2.—Moderate generalized cardiac enlargement.

Physical Examination.—The patient appeared to be chronically, but not acutely, ill. Her speech, motions, and response to questions were slow. The skin was pale, dry, and scaly. The hair on the arms, in the axillae, over the pubes, and in the eyebrows was scanty. Her face was oval, her eyelids puffy, and her lips thick. The heart was enlarged, with the left border of dullness 11 cm. to the left of the mid-sternal line. The blood pressure was 108/80.

Laboratory Examination.—The blood Kahn reaction was negative. The urine was normal. The hemoglobin was 57 per cent (Sahli); the erythrocytes numbered

3,200,000, and the leucocytes 6,800 per cubic millimeter. The differential leucocyte count was normal. There were 540 mg. of cholesterol per 100 c.c. of blood. On two occasions the basal metabolic rate was -41 per cent, and -37 per cent, respectively. The electrocardiogram before treatment was started (Fig. 1A) showed a heart rate of 62 per minute, with very small complexes and inverted T-waves in Lead I. A tracing taken six or eight hours before death (Fig. 1B), when the heart rate was 111 per minute, showed very bizarre QRS complexes in Lead I and fairly large, notched, upright QRS waves in Leads II and III. The QRS interval was slightly prolonged (0.11 sec.). The curve suggested partial right bundle branch block. Roentgenologic examination of the chest revealed moderate enlargement of all four chambers of the heart (Fig. 2). Measurements of the frontal plane area and transverse diameter of the heart by means of the orthodiagram and teleoroentgenogram agreed closely. When compared with the Eyster-P. C. Hodges tables, it was found that in the orthodiagram the frontal plane area was increased by 34 per cent, and the transverse diameter by 26 per cent; and that in the teleoroentgenogram the former was increased by 38

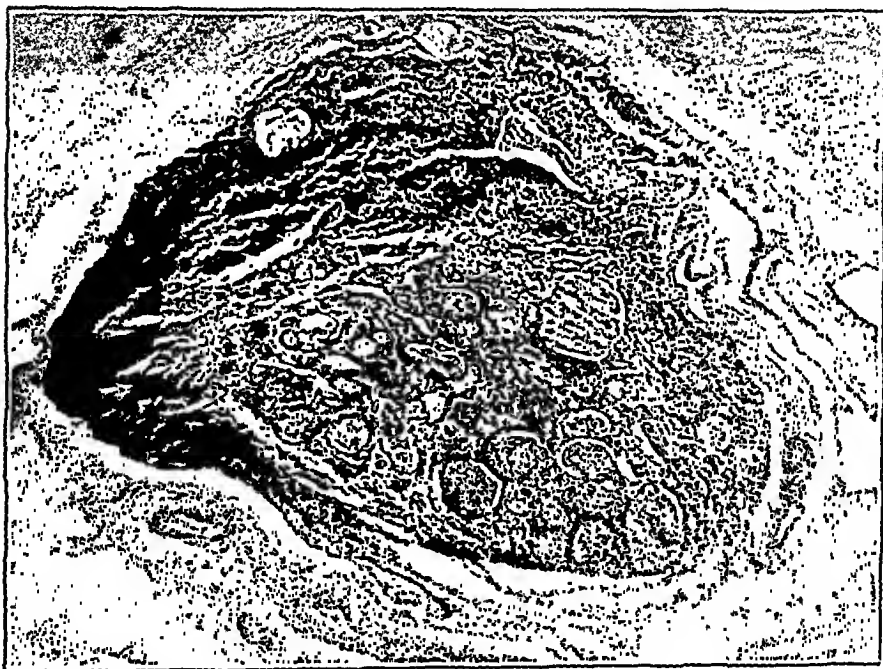


Fig. 3.—Largest nodule found in the thyroid gland.

per cent, and the latter by 23 per cent (a variation of 12 per cent above or below the calculated average is not considered abnormal).

Course in Hospital.—During the first few days the patient's temperature was subnormal. She was ambulatory and comfortable. On the second hospital day she received 0.12 gm. of desiccated thyroid, and 0.26 gm. daily for four days thereafter. Two days after treatment began she noticed a feeling of increased warmth, her temperature returned to normal, and she felt much better. On the third day the patient experienced typical anginal pain which was relieved by nitroglycerin. The two subsequent days were marked by an increase in the frequency and severity of the anginal attacks. The dose was then reduced to 0.065 gm. per day, and the drug was discontinued on the seventh day, after a total of 1.5 grams had been given. On the morning of the eighth day after the institution of thyroid therapy the precordial pain became constant and was not relieved by nitroglycerin or codeine and only slightly by morphine. The patient developed nausea, vomiting, cyanosis and extreme dyspnea; her pulse became imperceptible; her blood pressure fell so low that it

could not be measured; and râles appeared throughout both lungs. She died in the evening of the same day, fifteen days after admission.

Autopsy.—The thyroid showed diffuse atrophy with marked lymphocytic infiltration. The largest nodule in the thyroid gland is shown in Fig. 3. The heart weighed 190 gm.; its walls were soft and flabby. The coronary arteries were narrowed by extensive atherosclerosis and calcification. In the anterior and posterior branches of the left coronary there was a progressive narrowing as the apex was approached. There were both old and recent myocardial infarcts. One of the most recent was of large size, was surrounded by an active leucocytic infiltration, and appeared to be three or four days old (Fig. 4). No thrombosis or embolism was found. Massive pulmonary edema was present. The aorta showed atherosclerosis. It is of interest in view of the history of pain in the upper right quadrant which radiated to the scapula that there was no evidence of chronic cholecystitis.



Fig. 4.—Area of myocardial infarction showing necrosis and leucocytic infiltration.

DISCUSSION

Narrowing of the coronary arteries was found in our case and in all other reported cases in which an autopsy was performed. Bournville²⁷ and Fishberg²⁸ have produced evidence that there is a high incidence of arteriosclerosis in myxedema. The experiments of von Eiselsberg²⁹ on sheep and goats and of Shapiro³⁰ on rabbits showed that thyroidectomy predisposes to atherosclerosis. This may be related in some way to hypercholesterolemia, which is constant in myxedema, and is regarded by some as a valuable index of thyroid underactivity. Our patient's blood cholesterol level was high (545 mg. per 100 c.c.).

At present we have no way of judging how frequently patients with myxedema develop myocardial infarction, or whether the occurrence of angina pectoris and arteriosclerosis is more common in these patients

than in others of the same age. When the 108 proved cases of myxedema* which were seen in the University of Michigan Hospital between January, 1930, and March, 1937, were reviewed, it was found that angina pectoris had been present in two. The case reported herein is the only one of this series in which (1) the clinical diagnosis of myxedema was confirmed by metabolic studies and (2) an autopsy was performed. During this period of six years and two months the incidence of myxedema was 1 to 1313.

It has recently been shown that the administration of thyroid increases the blood velocity and the minute output of the heart; thus the myocardium must be supplied with more blood, and therefore it is reasonable to suppose that in our patient the narrowed coronary arteries were inadequate. As a result of this, it could be assumed that a localized area of necrosis of the myocardium developed. The acute cardiac failure was not associated with coronary thrombosis, and in only two of the five reported cases in which an autopsy was performed was thrombosis demonstrated.

It may be argued that in this case and in those previously reported, in all of which advanced atherosclerosis of the coronary arteries and angina pectoris were present, myocardial infarction might have developed had no thyroid substance been given at all. As Davis³¹ has aptly said, "One does not have to have myxedema to die of coronary thrombosis." It may well be that what we have observed is merely a coincidence, but it is nevertheless apparent that the number of reported cases of death from myocardial insufficiency in patients with untreated myxedema is remarkably small. Perhaps as the number of autopsies in cases of myxedema increases and more careful follow-up studies are reported, the frequency of this combination of diseases will be found to be significantly higher than our present records would indicate. At present we may conclude that a fatal outcome during active treatment is sufficiently common to justify repetition of the warning against the indiscriminate use of thyroid gland products, especially when the patient has retrosternal pain or other possible signs of heart disease.

SUMMARY

1. A review of the literature dealing with myxedema complicated by angina pectoris and myocardial infarction disclosed five cases in which autopsy showed that death was caused by acute coronary failure. These cases are summarized.
2. One case of myxedema and angina pectoris in which myocardial infarction developed during treatment with thyroid substance is reported.
3. Before giving thyroid gland products, a careful estimate of the cardiovascular status is necessary.

*There were 11 additional cases in which either the clinical manifestations were not well marked, or the clinical diagnosis was not substantiated by measurement of the basal metabolic rate.

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INCIDENCE AND TYPE OF HEART DISEASE IN SAN FRANCISCO SCHOOL CHILDREN*

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FOR the purpose of determining the incidence and type of heart disease in San Francisco school children, we have analyzed (1) the records of the Cardiac Diagnostic Center of the San Francisco Department of Public Health and (2) data obtained from study of a sample of the San Francisco school population.

STUDY OF TYPES OF HEART DISEASE OBSERVED AT THE CARDIAC DIAGNOSTIC CENTER

The present analysis of data obtained in the Cardiac Diagnostic Center covers a three-year period and makes use of the facilities described in Richter's report.¹ In that report it was explained that all school children are examined routinely by trained pediatricians of the San Francisco Department of Public Health. All cardiac suspects are referred either to their own physicians or to the Cardiac Diagnostic Center, which is administered by the Department of Public Health.

Roentgenographic, fluoroscopic, and electrocardiographic facilities are available. Regular follow-up investigations are made by members of the school nursing department, and these assist materially in ultimately obtaining accurate diagnoses. All cardiac disease suspects are examined by staff members on at least two visits, and many of the children included in our series were examined at six-month intervals throughout the three-year period. The criteria for diagnosis are those established by the American Heart Association.†

Statistical data are used in this study because, until rheumatic fever and its manifestations are made reportable, they afford the most satisfactory index of morbidity rates.

Table I is composite, showing the number of examinations made during each of the three years in the San Francisco schools and in preschool and well-baby conferences. Murmurs, fainting attacks, pulse irregularities, tachycardia, and hypertension are some of the symptoms for which these children are referred.

Table I also presents the diagnoses made by members of the staff of the Cardiac Diagnostic Center. It should be noted that although the number of children referred decreased over the three-year period,

*From the San Francisco Department of Public Health, and the Departments of Medicine and of Pediatrics of the University of California Medical School.

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†The San Francisco Cardiac Diagnostic Center is affiliated with the American Heart Association.

TABLE I

ANALYSIS OF DIAGNOSES MADE BY THE STAFF OF THE CARDIAC CENTER, 1931-1934

	1931-1932	1932-1933	1933-1934
Total school and preschool examinations	55,679	51,555	52,227
<i>Types of lesions</i>	<i>% of total no. of suspects</i>	<i>% of total no. of suspects</i>	<i>% of total no. of suspects</i>
Organic	162 29.4	98 21.8	61 20.9
Functional	179	137	151
Noncardiac	110	34	47
Diagnosis deferred	98	87	33
Total new heart disease suspects examined	549	356	292

the percentage of cases of organic heart disease among them remained remarkably constant.

Table II contains analyses of cases in which the examinations were made by one of the authors (Christie), of corresponding data from the investigation made in 1931 by Richter¹ at the same Cardiac Diagnostic Center, and of data obtained by Christie at the Children's Cardiac Clinic of the University of California.

TABLE II

TYPES OF ORGANIC LESIONS: COMPARISON OF INCIDENCE IN TWO SERIES STUDIED AT THE CARDIAC DIAGNOSTIC CENTER AND ONE SERIES AT THE UNIVERSITY OF CALIFORNIA CHILDREN'S HEART CLINIC

	TOTAL PATIENTS EXAMINED	TOTAL ORGANIC	TOTAL CONGENITAL	TOTAL RHEUMATIC	OTHER ETIOLOGY	PERCENTAGE OF CONGENITAL AMONG TOTAL ORGANIC
Cardiac Diagnostic Center (Christie, present report)	485	157	91	60	6	57.9
Cardiac Diagnostic Center (Richter ¹)	483	319	140	151	28	43.8
Children's Heart Clinic of the University of California* (Christie ²)	143	94	36	54	4	38.3

*Unselected patients referred to the Children's Heart Clinic, most of them for follow-up after hospital admission.

The 485 patients (Table II) examined personally in the Cardiac Diagnostic Center by one of the authors (Christie) were unselected and were studied in successive groups of 100 cases. The incidence of congenital heart disease in the entire group of cases of organic heart disease varied between 64.4 per cent in the first 100 and 51.5 per cent in the second 100; the average of the entire group was 57.9 per cent.

It should be noted that the percentage of cases of congenital heart disease among the cases of organic heart disease in the series from

the Children's Heart Clinic of the University of California (38.3 per cent) is lower than that in the two other series. This is undoubtedly due to the fact that a large number of the patients followed in this clinic are referred from the Pediatric Service of the University of California Hospital, where they have been observed during and after attacks of acute rheumatic fever. It is significant that in this group congenital heart disease constituted 38 per cent of the organic lesions.

Another probable explanation of the fact that the incidence of congenital cardiac disease in the patients examined at the Cardiac Diagnostic Center was higher than in those at the Children's Clinic of the University of California is that the former were, on an average, younger than the latter. For the same reason, in the study of a more representative cross section of the entire school population reported in the second portion of this paper, the figures obtained agree closely with those from the Children's Clinic of the University of California, but not with those from the Cardiac Diagnostic Center (Table III). The distribution by age groups illustrating this changing differential is presented later in Table VI and is likewise clearly shown in the integral graphic chart of heart disease based on a survey of the entire city by Geiger, Sampson, Miller, and Gray² (Fig. 1).

As Eastern authorities³⁻⁶ report that the incidence of congenital heart disease is 10 to 20 per cent of the organic lesions in their school populations, the high incidence of congenital cardiac disease in all three of the series shown in Table II gives evidence that there is a significant difference in the types of heart disease found in the eastern and western sections of the United States, provided similar diagnostic methods have been used in both regions. At the time our study was being made, we recognized this geographic discrepancy in incidence and therefore included in the congenital heart disease group only those cases in which the diagnosis was beyond question.

If we grant that congenital heart disease is due to a defect in germ plasm, there is no valid reason why it should occur more frequently in San Francisco than in any other locality. Since two observers working in three different clinics have noted an amazingly high percentage of congenital heart lesions in the groups of patients with organic heart disease, it seems logical to conclude that the incidence of rheumatic heart disease in this region is correspondingly low.

STUDY OF INCIDENCE FROM SAMPLING OF POPULATION

In the investigation of the group of cases reviewed above, no accurate estimate could be made of the actual incidence of cardiac disease in this particular unit of child population. This was due to the fact that it was impossible to determine how many of the school children with heart disease had been referred to the Cardiac Diagnostic Center

for study. Fifty per cent was considered a reasonable estimate both by Richter and ourselves (see footnote 2, Table VII).

The following study of a sample of population was made chiefly for the purpose of eliminating error in estimating the incidence of heart disease in the total population.

Following the method of sampling used by Cahan⁷ and others, 295 children in 30 of the 135 San Francisco schools, including one "health school" for handicapped children, were examined personally by one of the authors (Sampson). The total school population in San Francisco at the time of this study was 87,324. The 295 children examined had been selected by trained pediatricians during routine complete physical examinations of 18,607 children, i.e., the total number of pupils registered in the 30 schools. For various reasons, the incidence in 4 of the schools, including the health school, could not be accurately determined. Therefore, further selection was made of 197 children from the 13,338 pupils registered in 26 schools; this series represented, with possibly rare exceptions, all of the suspected cases of heart disease in this group.

While many of the children in the group had been examined in the School Cardiac Diagnostic Center in the Department of Public Health Building, or by private physicians, there were many others who had never been examined except in the school building during class hours. It is recognized that the possibility of error in diagnosis in difficult cases is greater when only the ordinary means of physical examination are used than when the roentgen ray and the electrocardiograph may also be employed. Furthermore, errors are likely to occur in all statistical analyses of groups of cases diagnosed without confirmation by autopsy, and the data must therefore be evaluated accordingly.

In our opinion, the figures on incidence, given in Table III, among the 197 children from 26 schools, are based on reasonably accurate diagnoses. These figures therefore represent at least a minimal estimate of the percentage of cardiac patients in the total school population. The individuals were students in the primary, intermediate, and high school grades, and ranged in age from 6 to 18 years. The incidence of organic heart disease in this group was 13 cases per thousand.

TABLE III

INCIDENCE OF CONGENITAL AND RHEUMATIC HEART DISEASE IN 197 CARDIAC DISEASE SUSPECTS FOUND AMONG 13,338 SCHOOL CHILDREN

SCHOOL POPULATION REPRESENTED	HEART DISEASE SUSPECTS	ORGANIC HEART DISEASE	RHEUMATIC		CONGENITAL		RATES PER 1,000 SCHOOL POPULATION		
			TOTAL	%	TOTAL	%	ORGANIC	RHEUMATIC	CONGENITAL
13,338	197	49	30	62	19	38	3.7	2.2	1.4

TABLE IV
DISTRIBUTION OF CASES OF VARIOUS TYPES OF HEART DISEASE BY AGE GROUPS IN 295 CARDIAC DISEASE SUSPECTS
AMONG 18,607 SCHOOL CHILDREN

AGE GROUPS INCL. (YR.)	POSITIVE DIAGNOSIS OF ORGANIC HEART DISEASE						DOUBTFUL DIAGNOSIS OF ORGANIC HEART DISEASE						POTENTIAL, RHEUMATIC		HYPER-TENSION		FUNCTIONAL, MURMURS OR ARRHYTHMIAS		TOTAL CARDIAC SUSPECTS
	RHEUMATIC		CONGENITAL		TOTAL		RHEUMATIC		CONGENITAL		TOTAL								
	TOTAL	%	TOTAL	%	TOTAL	%	TOTAL	%	TOTAL	%	TOTAL	%	TOTAL	%	TOTAL	%			
6-9	6	11.8	5	9.8	11	21.6	3	5.9	4	7.8	7	13.7	4	7.8	2	2.4	29	56.9	51
10-12	12	14.1	10	11.8	22	25.9	7	8.2	6	7.1	13	15.3	7	8.2	2	2.4	41	48.2	85
13-15	18	21.3	10	12.0	28	33.3	6	7.2	7	8.3	13	15.5	4	4.8	2	2.4	37	44.0	84
16-18	12	16.2	5	6.8	17	23.0	4	5.4	1	1.4	5	6.8	3	4.0	7	9.5	42	56.7	74
19	1	100.0			1	100.0													1
Total	49	16.6	30	10.2	79	26.8	20	6.8	18	6.1	38	12.9	18	6.1	11	3.7	149	50.5	295

The 295 cases of possible cardiac disease among 18,607 school children, which are analyzed in Table IV, include the group of children in the health school where a high percentage of the pupils registered are cardiac patients who have, for this reason, been selected for placement in this school. Such a concentration of cases does not affect the study of relative incidence of types of organic disease in this series of cases, but it does increase the apparent incidence of heart disease in the school population as a whole.

Table IV shows the comparative frequency of congenital and rheumatic heart disease, hypertension, and potential rheumatic and doubtful cardiac disease in various age groups. With the exception of two individuals, the groups covered inclusively the ages of 6 to 9, 10 to 12, 13 to 15, and 16 to 18 years. One child in the series was 5 years of age, and another 19 years of age.

Table V represents an attempt to analyze the nature of our sampling of school population. It will be noticed that in the group of heart disease suspects there were more children between 10 and 15 years, and fewer between 6 and 9 years than in the standard population for these age periods. The question arises as to whether this concentration of cases in a certain age period may introduce an error in our estimate of the number of cases of organic heart disease occurring in the various age groups (Table IV).

TABLE V

COMPARISON OF AGE DISTRIBUTION OF 295 CARDIAC DISEASE SUSPECTS EXAMINED WITH AGE DISTRIBUTION OF TOTAL POPULATION IN SIMILAR AGE GROUPS

AGE DISTRIBUTION OF SAN FRANCISCO POPULATION BY HENIDECADERS U.S. CENSUS 1930		ESTIMATE OF SELECTIVE AGE GROUPS BY INTERPOLATION FROM U.S. CENSUS FIGURES		AGE DISTRIBUTION IN SERIES OF 295 CASES STUDIED IN THE SAN FRANCISCO GROUP	
5-9 yr.	5.93%*	6-9 yr.	29%†	6-9 yr.	17.5%‡
10-14 yr.	5.68%	10-12 yr.	21%	10-12 yr.	28.8%
14-19 yr.	6.69%	13-15 yr.	23%	12-15 yr.	28.4%
		16-18 yr.	25%	16-18 yr.	25.0%
				19 yr.	0.3%

*Per cent of total population.

†Per cent of entire age group of 6 to 18 years.

‡Per cent of series of 295 cases studied.

Certain considerations lead to the belief that this disagreement in distribution of population does not influence materially the conclusions that may be drawn from the data presented in Table III. The incidence in our survey of organic heart disease occurring in children from the ages of 10 to 15 years agrees with estimates in other surveys. The common occurrence of "functional" murmurs between the ages of 6 and 9 years would account for the selection of a relatively large number of children of this age group as cardiac suspects, as was found in our study. Because organic heart disease is rare at this age, the

proportionately fewer cases found in this survey should not materially influence the total percentage of cases of organic heart disease in the entire age range studied.

It will be noted that four etiologic groups, other than those listed in Table II, have been added in Table IV, namely, doubtful rheumatic heart disease, doubtful congenital heart disease, potential rheumatic heart disease, and hypertension. Diagnoses were regarded as doubtful when the presence of a lesion could not be definitely established by means of the physical examination and history. Occasionally a case could not be classified with certainty as congenital or rheumatic, although it was recognized as one of organic heart disease. In such instances, the most likely diagnosis was made arbitrarily for the purpose of classification. Potential rheumatic heart disease was diagnosed when the history of rheumatic involvement was so recent that cardiac disease, although not sufficiently evident at the time of examination, possibly was present.

"Hypertension" was diagnosed when the systolic blood pressure was higher than 140 mm. Hg, but we realize that during the examination many of the children were apprehensive, and therefore it may be assumed that the initial readings in many instances were probably too high because of psychic as well as vascular instability. It is interesting that nearly 10 per cent of the children between the ages of 16 and 18 showed elevation of the systolic blood pressure, and that 64 per cent of them were boys. In this group, in contradistinction to true essential hypertension, the diastolic pressures were normal and the pulse pressures consequently high. Measurements such as 150/85 were common.

Little can be said of the frequency of "functional" murmurs in this particular group, for many children with such murmurs were not suspected of heart disease and therefore were not referred.

In the school survey (Table III), as at the Cardiac Diagnostic Center, the incidence of congenital heart disease was unusually high. It is significant that the figures show an approximately equal proportion of cases of rheumatic and congenital heart disease up to the age of 12 years, instead of the rising predominance of rheumatic heart disease between the ages of 10 to 12 years which has been observed by others (Tables IV and VI).

Table VI shows the proportionate incidence of rheumatic and congenital cardiac disease in cases of organic heart disease in various age groups.

Rheumatic heart disease was divided equally between the sexes (49 per cent boys, 51 per cent girls), which agrees with Christie's figures for northern California (48 per cent and 52 per cent, respectively).

Only 6, or less than 10 per cent, of the children with rheumatic heart disease or potential rheumatic heart disease had had their pri-

TABLE VI

PROPORTIONATE INCIDENCE, BY AGE GROUPS, OF RHEUMATIC AND CONGENITAL HEART DISEASE IN 79 CASES OF ORGANIC HEART DISEASE POSITIVELY DIAGNOSED IN 295 CARDIAC DISEASE SUSPECTS AMONG 18,607 SCHOOL CHILDREN

AGE GROUPS (INCLUSIVE)	RHEUMATIC		CONGENITAL		TOTAL NO. OF CASES
	NUMBER	PER CENT	NUMBER	PER CENT	
6-9 yr.	6	54.5	5	45.5	11
10-12 yr.	12	54.5	10	45.5	22
13-15 yr.	18	65 +	10	35 -	28
16-18 yr.	12	68.5	5	31.5	17
19 yr.	1				1
Total	49	62	30	38	79

many acute rheumatic attack before they came to San Francisco. This fact is important in comparing the incidence of rheumatic fever in this locality with that in other parts of the country. More instances might have been discovered if careful histories had been obtained from the parents in every case, but this was not always possible.

Table VII gives figures from a review of the literature dealing with the incidence of organic and rheumatic heart disease in school populations of the middle, western, and eastern United States, as well as Great Britain. The marked geographic differences in the incidence of organic and rheumatic heart disease in these localities may be noted. By statistical analyses of two series of cases, using in one instance an indirect and in the other a direct method of estimation, the low incidence for San Francisco school children is shown.

TABLE VII

INCIDENCE OF ORGANIC AND RHEUMATIC HEART DISEASE IN SCHOOL POPULATIONS OF THE UNITED STATES AND GREAT BRITAIN

LOCALE	NO. OF CHILDREN EXAMINED	ORGANIC HEART DISEASE PER 1,000	RHEUMATIC HEART DISEASE PER 1,000
San Francisco (Authors' Table III)	13,338*	3.7	2.20
San Francisco, 1921-1934 (Authors' Table II†)	86,082	3.7	1.55
Cincinnati, 1930 ⁹	6,960*	3.7	2.90‡
New York City, 1921 ³	44,000*	5.0	4.30
Boston, 1927 ⁵	119,337*	5.2	4.60
England and Wales ¹⁰	598,167*	7.0	
Chicago, 1923 ¹¹	158,826*	9.0	7.20‡
Philadelphia, 1929 ⁴	10,333*	9.1	8.20
New York, 1918-1922 ¹²	1,336,343*	13.9	
Gloucestershire, 1927-1930 ¹³	53,501*		1.03
Somerset, 1927-1930 ¹³	42,804*		2.17
Bristol, 1927-1930 ¹³	54,673		7.72
New Mexican Indians ¹⁴	1,019		5.00
Northern Indians ¹⁴	688		45.00
Philadelphia ⁷	33,293	6.0	3.90
New Haven ¹⁵	5,758		48.10

*Figures do not include a preschool group.

†Calculated from Table 1 on the basis that there were 321 cases of organic heart disease in a school population of 86,082 from 1921 to 1934, inclusive. It is assumed that patients examined at the Cardiac Center represent the heart disease suspects from the Well-Baby Conference plus 50 per cent of those examined at school.

‡Computed on a basis of 80 per cent of all cases of heart disease.

SCLEROSING OF VARICOSE VEINS BY LIGATION AND ONE MASSIVE INJECTION OF SODIUM RICINOLEATE (SORICIN)*

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TO THE best of our knowledge, the earliest attempts to obliterate varicose veins were made by Provatz¹ in 1851. These attempts were somewhat successful, but there were many reactions and infections, and some fatalities. DeLore,² in 1894, first demonstrated the action of drugs which produce obliteration in the veins. Since the beginning of this method of treatment of varicose veins many types of solutions have been used with varying degrees of success.

The action of sclerosing agents has been carefully studied by animal experimentation and biopsy. These observations indicate that following the formation of an adherent fibrotic clot there is sufficient irritation to cause destruction of the intima of the vein. This is followed by the formation of a firm deposit of fibrin and blood platelets, resulting in the formation of a dense clot extending into the smaller vein which leads into the varicosity.

Figs. 1 to 4, photomicrographs of the cross section of the ear vein of a rabbit, show the effect of a 2 per cent solution of sodium ricinoleate (soricin) at intervals of fifteen minutes to twenty-four hours. It appears from the photomicrographs that the clotting of the blood is an immediate effect due to coagulation of the red cells and that it precedes the injurious effects on the lining of the vein. This clotting is a sudden event and does not follow the usual course of an ordinary, slowly developing ante-mortem thrombus. Within an hour after the injection of sodium ricinoleate, destruction and desquamation of the lining endothelium occur. Within twenty-four hours there is complete destruction of the intima of the vein, with some degenerative changes taking place in the surrounding tissue, probably due to an extension of the material out of the venules into the tissue spaces.

The chief danger encountered in this procedure is the possibility of deep vein sclerosis. This, we believe, is diminished by changing the posture of the patient immediately after the injection so that the foot becomes dependent. As soon as the wound is closed, the patient gets up and walks about. In our series there has been no obliteration of the deep veins. We attribute this to the fact that we make our patients become active at once and that we use a dilute solution. This is further diluted by the blood and cannot cause much damage to the intima of the vein thereafter.

*From the Peripheral Vascular Clinic of the North Side Unit, Youngstown Hospital Association.

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The sclerosing solution used in our work is a 2 per cent solution of sodium ricinoleate prepared in accordance with the directions of Rider.³ The drug in this solution is approximately 98 per cent pure sodium

Fig. 1.

Fig. 2.

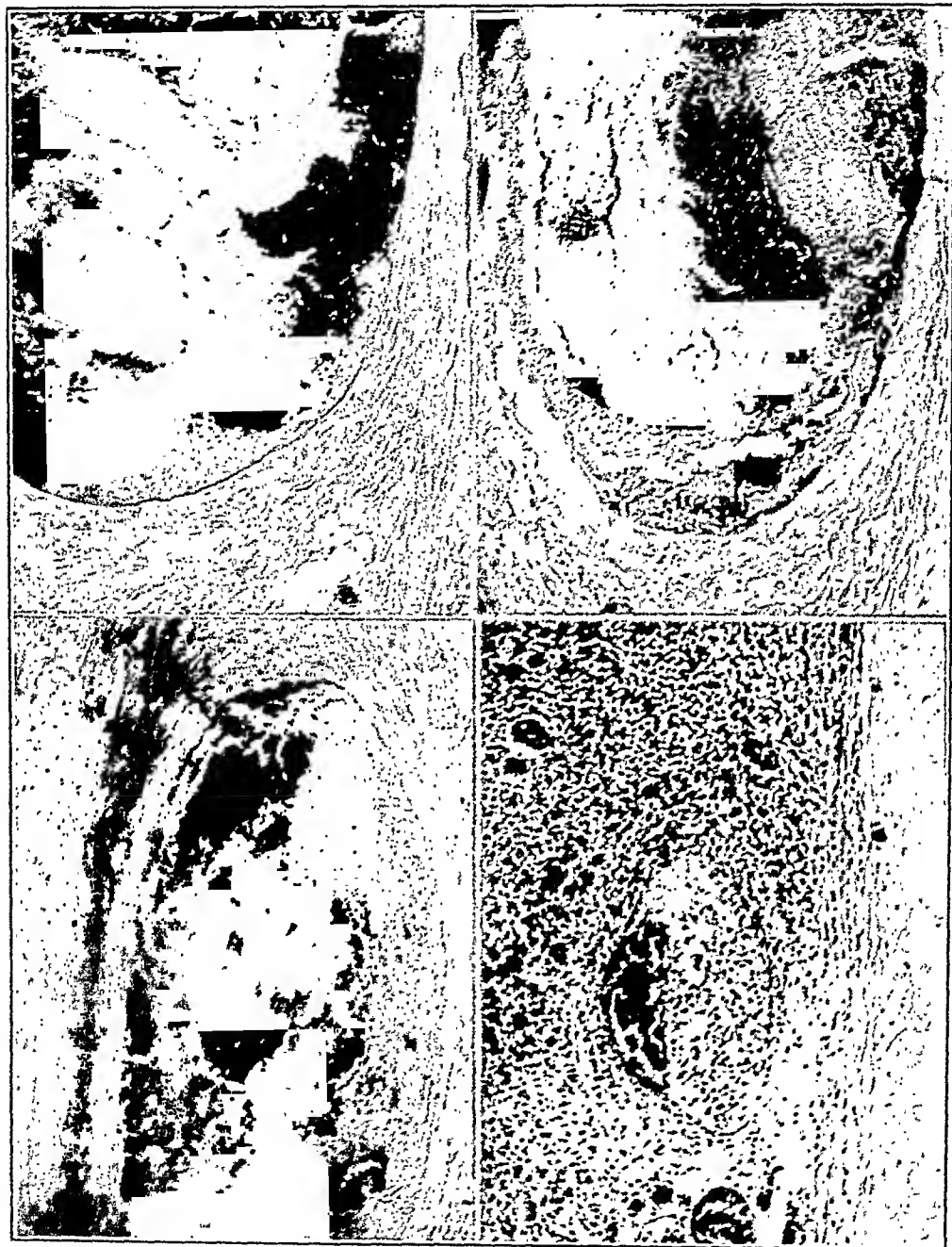


Fig. 3.

Fig. 4.

Fig. 1.—Cross section of ear vein of rabbit fifteen minutes after injection of sodium ricinoleate.

Fig. 2.—Cross section of ear vein of rabbit one hour after injection of sodium ricinoleate.

Fig. 3.—Cross section of ear vein of rabbit six hours after injection of sodium ricinoleate.

Fig. 4.—Cross section of ear vein of rabbit twenty-four hours after injection of sodium ricinoleate.

ricinoleate, with small amounts of sodium oleate and sodium linoleate. We feel that one distinct advantage in the use of sodium ricinoleate is the fact that it is a known, stable compound, the composition of which can be controlled within very narrow limits. The 2 per cent solution has a pH which has been adjusted to 8.0.

Froehlich and Henrickson⁴ report the use of 5 per cent sodium ricinoleate in the treatment of varicose veins in 300 patients. Their method was to give a preliminary injection of 1 c.c. into a small loop of the vein as a test to determine whether or not the patient was sensitive to sodium ricinoleate. If no sensitivity was evidenced, a 5 c.c. dose was used in a sufficient number of injections (averaging three to four in number) until all veins were sclerosed.

Postlethwaite⁵ employed a 2 per cent solution of sodium ricinoleate, using only small amounts of the solution and making repeated injections until the entire vein became sclerosed.

Riddle⁶ reported the use of 10 per cent sodium ricinoleate and found that it was effective even when 10 per cent sodium morrhuate or invert sugar had failed.

McPheeter⁷ states that 5 per cent sodium ricinoleate is as good as sodium morrhuate but that it is a little stronger and gives more of a reaction. For this reason he is now using 2 per cent sodium ricinoleate in the larger veins and 0.5 per cent in the superficial vein ruptures.

Johnston⁸ reports the use of a solution of 5 per cent sodium ricinoleate with ligation of the great saphenous vein and its branches at the femoral opening. He stresses the importance of ligating the branches to prevent recurrence and canalization. We believe that, if marked adhesions or lymphatic blockage are present, they contraindicate wide dissection to ligate the branches because the wound does not heal readily and marked seepage results. The destruction of the lymphatics by dissection results in the increased production of edema which persists for a long time and prevents further injection of the vein, should this be necessary. Johnston⁸ also stresses the importance of testing the arterial circulation, with which we are in accord.

In the treatment of varicose veins, we have not been satisfied with the fractional injection of small quantities at the site of the varicosities. The disadvantages of this method of treatment consist of a period of disability and discomfort, lasting from four to seven days after each treatment, and a multiplicity of injections requiring from three to six months, accompanied by numerous periods of disability and discomfort scattered throughout the treatment. There is also to be considered the danger of the development of sloughs at the site of the injection.

Because of these disadvantages, we have adopted a somewhat different procedure in selected patients who have reacted satisfactorily to the Trendelenburg and Perthes tests, and have also had a thorough examina-

tion of the arterial system, including oscillometric readings, surface temperature readings, and Collens-Wilensky and Buerger tests.

In the Trendelenburg test the patient is placed in the decubitus position and the extremity is raised to empty the veins. A tourniquet is placed above the knee. The patient then stands. Quick filling of the veins from below upwards means that the communicating vein valves are incompetent and that there is overflow from the deep veins into the superficial ones. When the tourniquet is released, if the saphenous vein fills rapidly from above as soon as the patient stands up, it indicates that the valves at the saphenofemoral junction are incompetent. The latter is a positive Trendelenburg test. A combination of the two is a Trendelenburg double test.

The Perthes test shows whether or not the femoral vein is patent. With the patient standing a tourniquet is placed above the knee just tight enough to cut off the superficial venous return. The patient then walks about the room several times. If the deep venous return is not adequate, pain will soon be experienced throughout the leg. If the deep veins are open, the dilated superficial veins tend to collapse and no pain will be produced. The collapse of the veins is due to the sucking out of the blood by muscular contraction. The blood is drawn through the communicating veins into the femoral system and then up through the femoral vein.

The Buerger test is performed by having the patient assume the supine position, elevate the legs, and flex and extend the ankle rapidly. The foot is observed for blanching, and any pain or cramp in the calf is noted.

The Collens-Wilensky test is performed as follows: The patient lies down and the foot is elevated until the superficial veins are collapsed. Then the foot is quickly lowered over the side of the bed and the time for filling of the superficial veins on the dorsum of the foot is noted. The normal filling time is from five to seven seconds.

COMPARISON OF METHODS OF TREATMENT

The treatment consisted in Group 1 of injections of various drugs and in Group 2 of ligation of the great saphenous vein and its branches, followed by multiple injections of 2 per cent sodium ricinoleate. Group 3 consisted of patients who were treated by ligation of the great saphenous vein and its branches, together with massive injections of a 2 per cent solution of sodium ricinoleate into the distal portion of the vein. This constitutes what we consider to be the most satisfactory method thus far described.

Group 1.—This group comprised 26 patients, all of whom showed a chemical thrombophlebitis at the site of injection. They were treated with multiple injections of various solutions: namely, sodium salicylate 30 per cent, averaging 207 c.c.—13 cases; sodium morrhuate, averaging 76 c.c.—9 cases; quinine hydrochloride and urethane, averaging 17 c.c.—4 cases. There were no ligations of the great saphenous vein in this group. Recurrence and canalization after two years occurred in 38½ per cent of the cases.

Group 2.—This group consisted of 78 patients who were treated by ligation of the great saphenous vein and its branches and multiple injections of 2 per cent sodium ricinoleate, averaging 48 c.c. There was no recurrence nor canalization after one and one-half years.

Group 3.—This group consisted of 31 patients who were treated by ligation of the great saphenous vein and its branches, when feasible, and injection of 2 per cent sodium ricinoleate, averaging 17 c.c. There was no recurrence or canalization after one year. In addition, iontophoresis of acetyl-beta-methylcholine chloride (mecholy) and the application of the intermittent venous compression cuff (Collens-Wilensky) were used.

In Group 3, the new procedure was adopted only in selected cases, the criteria for the selection of which will follow.

The results are shown graphically in Charts 1, 2, and 3.

Group 1.—There were 9 ulcers (3 bilateral) in this group. The method of treatment employed did not lead to healing after one year's time. Relief of postinjection pain was never accomplished in less than



Fig. 5.

Fig. 6.

Fig. 7.

Fig. 5.—F. W., aged 52 years, a tailor. Varicose veins for fifteen years. Treated by ligation of great saphenous vein and injection of 27 c.c. of a 2 per cent solution of sodium ricinoleate.

Fig. 6.—F. W. Disability for one week. Marked induration and periphlebitis, chemical phlebitis. Mecholy by iontophoresis, and Collens-Wilensky cuff, daily for one week, beginning forty-eight hours after injection and ligation.

Fig. 7.—F. W., six weeks later.

two weeks. In 11½ per cent of the cases disappearance of periphlebitis was evidenced within two weeks after completion of treatment.

Group 2.—There were 22 ulcers in this group in which healing occurred within twelve weeks (6 per cent of cases). Eight and one-half per cent of the patients were relieved of pain within one week. In 24 per cent of the cases the periphlebitis disappeared within one week.

Group 3.—There were 7 ulcers in this group, all of which were healed within nine weeks; 87 per cent of the patients were relieved of pain

within one week. In 84 per cent of the cases periphlebitis disappeared in less than one week, averaging four days.

In the treatment of superficial vein ruptures we have employed a 0.25 per cent to 0.5 per cent solution of sodium ricinoleate in doses of 0.25 to 0.5 c.c., and we have found that the sclerosing effects leave less discoloration than was experienced with any other solution. McPheeter⁷ reports similar results. This good cosmetic effect is especially appreciated by the younger female patients.



Fig. 8.

Fig. 9.

Fig. 8.—C. R., aged 48 years, a laborer. Varicose veins for twelve years, ulceration for four years. Treated by ligation of great saphenous vein and injection of 22 c.c. of a 2 per cent solution of sodium ricinoleate. Mecholyt by iontophoresis, and Collens-Wilensky cuff, daily for two weeks, beginning forty-eight hours after injection and ligation. Ulcer healed. Disability lasted four days.

Fig. 9.—C. R., anterior view.

SELECTION OF CASES AND CONTRAINDICATIONS

Patients with varicosities which extended above the knee and those with varicose ulcers were selected for ligation. These patients were required to have adequate deep venous circulation as shown by the Perthes test.

In selecting the cases in Group 3, we excluded the aged (past 60 years), the very obese, high-strung nervous patients, and those with very chronic extensive, infected ulcers. All subjects were tested for the pres-

ence of latent infection by checking leucocyte counts and blood sedimentation time. Wassermann tests and complete urinalyses were made routinely. The presence of diabetes is a contraindication unless it is well under control. In patients with syphilis, antisyphilitic treatment is pushed energetically, and, when the ulcer shows healing, the treatment is conservative, namely, ligation and fractional injection.

This group does not include those patients who had, in addition to involvement of the great saphenous vein, varicosities of the lesser saphenous vein. These patients were placed in Group 2, inasmuch as they were subjected to ligation of the great saphenous vein and subsequent multiple injections.

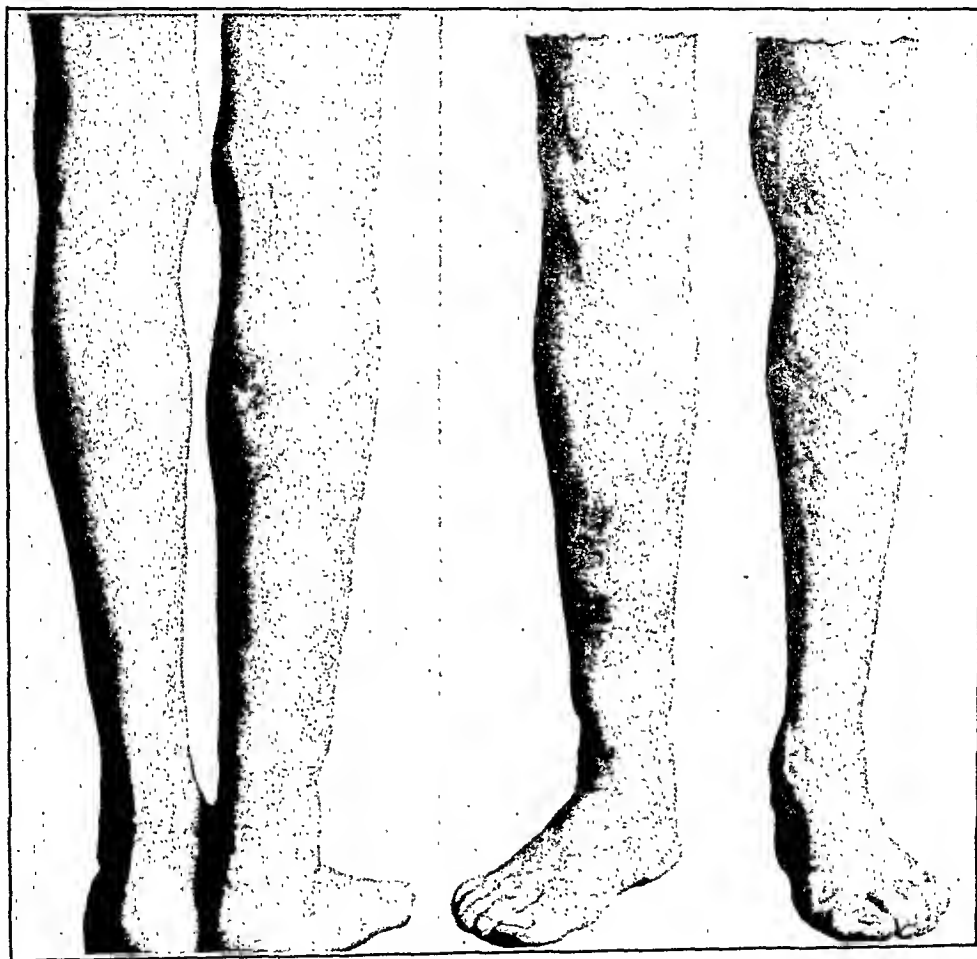


Fig. 10.

Fig. 11.

Fig. 10.—C. R., posterior view two months later.

Fig. 11.—C. R., anterior view made at same time as Fig. 10.

TECHNIQUE

The technique was similar to that of Faxon⁹ and Johnston,⁸ namely, ligating and cutting the great saphenous vein near its entrance to the femoral and also ligating and cutting such branches as present themselves, avoiding undue dissection. The branches encountered are the superficial external pudendal, the superficial external epigastric, the superficial circumflex iliac, the internal superficial femoral, and the external superficial femoral veins.

A syringe filled with the desired amount of a 2 per cent solution of sodium ricinoleate is fitted with a fairly large bore needle (20 gauge), and the needle is inserted

distal to the first ligature. The suture placed around the distal portion of the vein is tied over the needle but is not tightened until after the solution is injected and the needle withdrawn. The amount of sodium ricinoleate used varied from 6 to

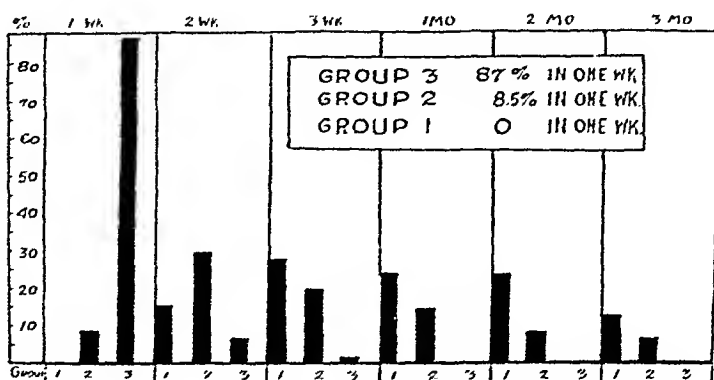


Chart 1.—Relief of pain.

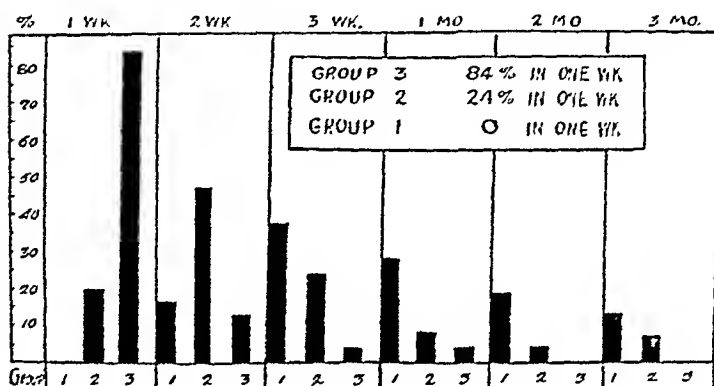


Chart 2.—Disappearance of periphlebitis.

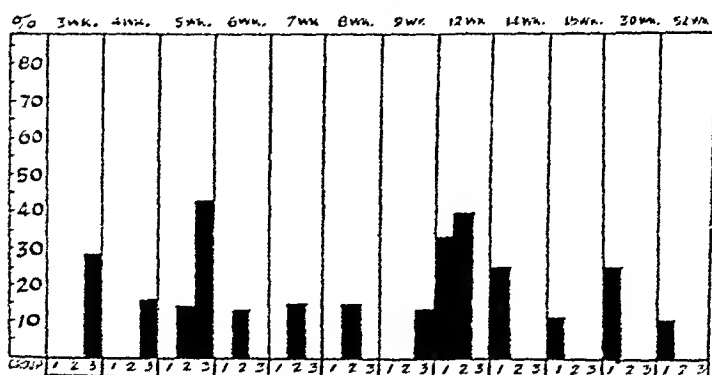


Chart 3.—Healing of ulcers.

Group 1, recurrence of varicose veins and canalization, 38.5 % (two years); Group 2, recurrence of varicose veins and canalization, 0 (one and one-half years); Group 3, recurrence of varicose veins and canalization, 0 (one year).

30 c.c. The vein is then ligated and severed between the distal and proximal ligatures. The proximal segment of the vein is doubly ligated as an added safeguard.

This method of treatment was employed in 31 patients and produced complete obliteration of all varicosities of the great saphenous tree.

AFTEREFFECTS AND REACTIONS

When the primary burning disappears, within a few minutes after injection, patients may get up. They usually complain of a "leadens," "heavy" feeling of the extremities. They claim that the legs feel "drawn" and "tight." Within twelve hours, a brawny induration of the entire extremity ensues. Within twenty-four hours, the skin over the vein becomes ecchymotic and the periphlebitis (due to penetration of the solution into the venules and tissue spaces) is quite painful. Within forty-eight hours some edema usually appears. Treatment of these two developments has consisted of application of the intermittent venous compression cuff (Collens and Wilensky¹⁰) and iontophoresis of acetyl-beta-methylcholine chloride (mecholy1).¹¹ As a rule, the pain and edema last from two to four days. The patient is usually not disabled and continues at his work.

AFTERTREATMENT

The day following injection, the patient returns to the clinic and receives a treatment by iontophoresis. This was instituted because it was noted that, when patients with severe periphlebitis and chemical thrombophlebitis were subjected to this treatment, following multiple injections (Group 1) without ligation, they responded with complete relief of pain, stiffness, and induration of the parts involved. On the next day, the intermittent venous compression cuff (Collens and Wilensky¹⁰) is applied to the thigh for a period of one hour or more depending upon the amount of discomfort produced and whether the edema increases. This treatment is given daily and is continued as long as there is periphlebitis and swelling.

The treatment of the ulcer also includes acetyl-beta-methylcholine chloride¹¹ by iontophoresis, the ulcer area being covered with vaseline gauze. After treatment, the ulcer is covered with a dressing of N:N-dichloroazodicarbonamidine (azochloramide) in oil. Activity is encouraged, and no elastic bandages are applied. In the last three cases, the azochloramide was made up into an ointment which contained 50,000 units of vitamin D to the ounce. This seemed less irritating and did not require vaseline protection.

DISCUSSION

After having tried various solutions for sclerosing varicose veins by injection, we resorted to a 1 to 5 per cent solution of sodium ricinoleate.

We have found that a 2 per cent solution of sodium ricinoleate is best suited for our purposes, inasmuch as adequate thrombosis is obtained without producing too severe a local reaction. In superficial vein ruptures 0.25 per cent to 0.5 per cent solutions were most satisfactory in our experience. Sclerosing effects were produced without undue discoloration.

The local reactive symptoms encountered, such as periphlebitis and painful thrombophlebitis, were treated at home by local applications of

aqua Hamamelidis compresses, with encouraging results. The induration about the veins was quickly relieved with acetyl-beta-methylcholine chloride¹¹ by iontophoresis. Paradoxical as it may seem, the edema produced was quickly reduced (in twenty-four to forty-eight hours) by the use of the intermittent venous compression cuff (Collens and Wilensky¹⁰) for two to six hours per treatment, forty-eight hours after ligation and injection. This is not begun sooner because the vein has been ligated, and there is danger of forcing off the ligatures. The result obtained may be explained by the facts that the venules were kept canalized and the edema was reduced by forcing an increased volume of blood through them.

Noting the good results obtained by the use of these agents in small veins, we injected the whole tree and treated the reactions in the same manner with surprising and satisfactory results.

SUMMARY

A method of treatment of varicose veins by injection of large amounts of 2 per cent sodium ricinoleate solution in the entire venous tree, together with ligation of the saphenous vein, is presented. The amount injected may vary from 6 to 30 c.c., depending upon the nature of the case. Cases should be carefully selected, excluding patients who have syphilis, diabetes, old, extensive, infected ulcers or who are extremely obese, or senile (past 60 years old). With this method, the length of treatment and time of disability have been considerably shortened, and the results appear more satisfactory than those following the use of other sclerosing solutions and other methods of procedure in the treatment of varicose veins.

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THE MONOCARDIOGRAPH*

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WILLEM EINTHOVEN, through his invention of the string galvanometer, provided us with an instrument of great sensitiveness and accuracy which made it possible to record and study the small electric currents generated by the hearts of animals and man. Physicians and physiologists, prominent among whom was Einthoven himself, soon laid the foundation of what has since been known as electrocardiography.

Electrocardiography was fortunate in its inception because it was established on a solid groundwork of well-developed physical and mathematical science. Although there was, and still is, some doubt as to the precise means by which the heart muscle generates an electric current, nevertheless, once such a current is generated, the mechanism of its spread and the recording of its characteristics are subject to precise and well-known physical laws. The use of the two arms and the left leg as contact or leading-off points provided constant and readily reproducible curves. These curves, as Einthoven showed, were readily susceptible to mathematical analysis.

This analysis is based on the fact that at any instant the differences of potential between the three leading-off points bear a simple relationship to one another, namely, that the difference of potential between the right arm and the left leg (known as Lead II) is equal to the sum of the potential difference between the right arm and the left arm (Lead I) and the potential difference between the left arm and the left leg (Lead III). The relationship can perhaps be better understood if we state it as follows: There are two ways of measuring the difference of potential between two points (right arm and left leg). We may either measure the difference of potential directly (Lead II), or we may select a third point (left arm) and measure the differences of potential between our original two points and this third point (Leads I and III), adding together these two differences. Obviously our answer will be the same whichever method we use.

Since the voltage of Lead II must at any instant be exactly equal to the sum of the voltages of Lead I and Lead III, Einthoven represented this fact graphically by means of a geometrical figure. He chose an equilateral triangle as the proper figure because the projections on the sides of an equilateral triangle of any line drawn within the triangle are so related that one projection is equal to the sum of the other two.†

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†This is, of course, a simplified and partial statement of the more general proposition that the projection of a line upon any side of an equilateral triangle equals the sum or difference of the projections of the same line upon the other two sides of the triangle.

Through the use of Einthoven's triangle it was possible to make a graphic representation of the voltage of the three leads of the electrocardiogram at any instant. By means of this triangle, mathematical and geometrical analysis of the electrocardiogram was facilitated. The two arms and the left leg are not placed at the apices of an equilateral triangle, and their actual spacing varies in different individuals. The use of an equilateral triangle does not presuppose that the leading-off points are equidistant from each other, but depends on the geometrical properties of such a triangle and its suitability for graphic representation of the electrocardiogram.

It would be desirable for an exact geometrical analysis of the electrocardiogram to know the exact distance of each electrode from the heart and from the other two electrodes, as well as the exact electrical characteristics and location of all the body tissues involved in conducting the electrical impulses from the heart to the electrodes. These various factors would have to be evaluated each time an electrocardiogram was taken. Obviously, even if we knew how to make all these evaluations, the enormous amount of work involved would be disproportionate to the results obtained. The use of the equilateral triangle for spatial analysis of the electrocardiogram involves an approximation which is unavoidable and one that varies with the electrocardiograms of different individuals. It has, however, the advantage of practicality and relative ease of application, and, provided the analyst bears in mind the necessary limitations of the method, Einthoven's triangle furnishes us with a valuable tool.

As a result of studying the mathematical and geometrical relationships previously discussed, the author devised and published in 1920¹ a method of analyzing the electrocardiogram. This method, based on Einthoven's triangle, consisted of measuring the voltage of the three standard leads at intervals of 0.01 second, and then plotting these voltages as a consecutive series of points on a polar curve. When these points were joined together as a smooth curve the result was a single curve embodying the three leads of the electrocardiogram. This single curve was called the monocardigram.

The production of a monocardigram from an ordinary electrocardiogram involved many hours of careful work. A photographic enlargement or camera lucida drawing of each lead was essential for accuracy. These enlargements were then measured at intervals of 0.01 second, and the measurements arranged, by trial and error, so that for every moment of the cardiac cycle Lead II equalled the sum of Lead I and Lead III. After mathematical computation the successive points of the monocardigram were plotted on coordinate paper and connected with a fairly smooth curve.

The monocardigram gave information of such value that the labor involved in producing this curve seemed justified, but, in addition to

the laboriousness of the process, the method described had several other drawbacks. In the first place, the use of the method required such a high degree of technical training and judgment that it could not readily be delegated to assistants, and therefore could not be made a routine procedure. In the second place, the final result was a curve drawn by hand on coordinate paper—a curve which might give the impression of being artificial, inaccurate, and not closely related to actual cardiac events. To many who did not concern themselves with technical details, the standard electrocardiogram seemed closer to reality than did the monocardigram, which impressed them as a derived “imaginary” curve.

Both of these objections would be met and overcome if an instrument—the monocardigraph—could be devised to inscribe the monocardigram automatically, without mathematical calculation and without the interposition of the human factor. This monocardigraph should be so designed that when connected to the two arms and the left leg it would produce a single polar curve instead of the three standard leads. This polar curve could be recorded photographically in a manner somewhat analogous to the recording of the electrocardiogram. For such an instrument a string galvanometer was not suitable. A combination of two mirror galvanometers might serve the purpose of combining two or more leads, but the available mirror galvanometers were slow and otherwise unsatisfactory for recording the electrical output of the heart. The cathode-ray oscillograph offered the best prospect of success in the construction of a monocardigraph.

The cathode-ray oscillograph operates by means of a beam of electrons which impinges on a fluorescent screen, making a small bright spot in much the same way that the narrow beam of flashlight is thrown against a wall. This beam of electrons can be deflected electrically so that the bright spot on the fluorescent screen moves and produces a curve which can be recorded photographically. The cathode-ray oscillograph has no appreciable lag, and will respond faithfully to vibrations much more rapid than those recorded in the electrocardiogram. It is not, however, as sensitive to small currents as is the string galvanometer, and therefore the electrical output of the heart must be amplified before it is led to the cathode-ray oscillograph.

In 1924 the author succeeded in producing an instrument which consisted essentially of two three-stage amplifiers actuating a cathode-ray oscillograph. When the two arms of a patient were connected to one amplifier and the left arm and left leg were connected to the other amplifier, the cathode-ray oscillograph produced a curve resembling the monocardigrams which had previously been drawn by hand. This curve varied in shape for different individuals, varied in direction when the heart was rotated by forced respiration, and varied in character for extrasystoles of different types. It had, however, serious drawbacks.

In the first place, it was not bright enough for good photographic recording, and the spot was too fuzzy and ill defined for accurate measurement. In the second place, because of the construction of the cathode-ray oscillograph, it was possible to use only two leads (namely, Leads I and III), and this introduced considerable error into the curves. Either a radical modification in the construction of the cathode-ray oscillograph would be necessary, or an entirely new instrument would have to be devised.

Nevertheless, this crude monocardigraph, consisting of two amplifiers and a cathode-ray oscillograph, was suitable for a demonstration of the validity of the method and of the objective existence of the monocardigram. By means of this apparatus a demonstration of these points was made to a number of physicians, and, as a result of this demonstration, the Rockefeller Institute late in 1926 provided a grant for the construction of a better monocardigraph.

In 1926 the author began the construction of experimental galvanometers so designed that they would respond to three independent electrical currents. With the valuable assistance of J. F. Pattee, a galvanometer was finally designed and constructed which was capable of responding simultaneously to three separate electrical currents and had the required speed and accuracy for the recording of a monocardigram. This galvanometer reflected a small, sharp, brilliant spot of light excellently suited for accurate photographic recording. It was actuated by three amplifiers, one corresponding to each lead of the electrocardiogram, and produced a curve indistinguishable from the mathematically derived monocardigram. In 1931 this galvanometer with its amplifiers was demonstrated at the New York Academy of Medicine Graduate Fortnight. Since that time, the monocardigraph, of which this special galvanometer is the essential part, has been in almost constant use.

TECHNICAL DESCRIPTION

The monocardigraph consists of the following parts: (1) An *amplifier* which amplifies without appreciable distortion the currents obtained from the body, and actuates (2) a *galvanometer* which responds simultaneously to three currents corresponding to the three leads of the electrocardiogram. The deflections of this galvanometer are magnified by means of (3) an *optical system* and recorded upon (4) a *camera*. A detailed description of these parts follows.

1. The *amplifier* consists essentially of three similar three-stage amplifiers as illustrated in Fig. 1. To the three leading-off points of the body electrodes are applied as in ordinary electrocardiography. From these electrodes the voltages are brought to three similar wire-wound 300,000-ohm resistors which are matched within 1 per cent. By making these resistors equal, the symmetry of the system is preserved at this point. The same extremities of these resistors are connected to the grids of the first tubes of each amplifier. The other extremities are connected together through grid-bias cells which are grounded. This is the only point at which the input circuit is grounded. The patient is not connected to the ground or a shield at any point. This arrangement makes the amplifiers very sensitive to induction and necessitates careful shielding and elimination of stray fields.

The first two tubes of each amplifier are type 36 screen-grid radio tubes. They amplify the voltage about 2,500 times. The amplified voltage is fed to the third tube (171-A power tube). The third tube transforms the voltage into the desired

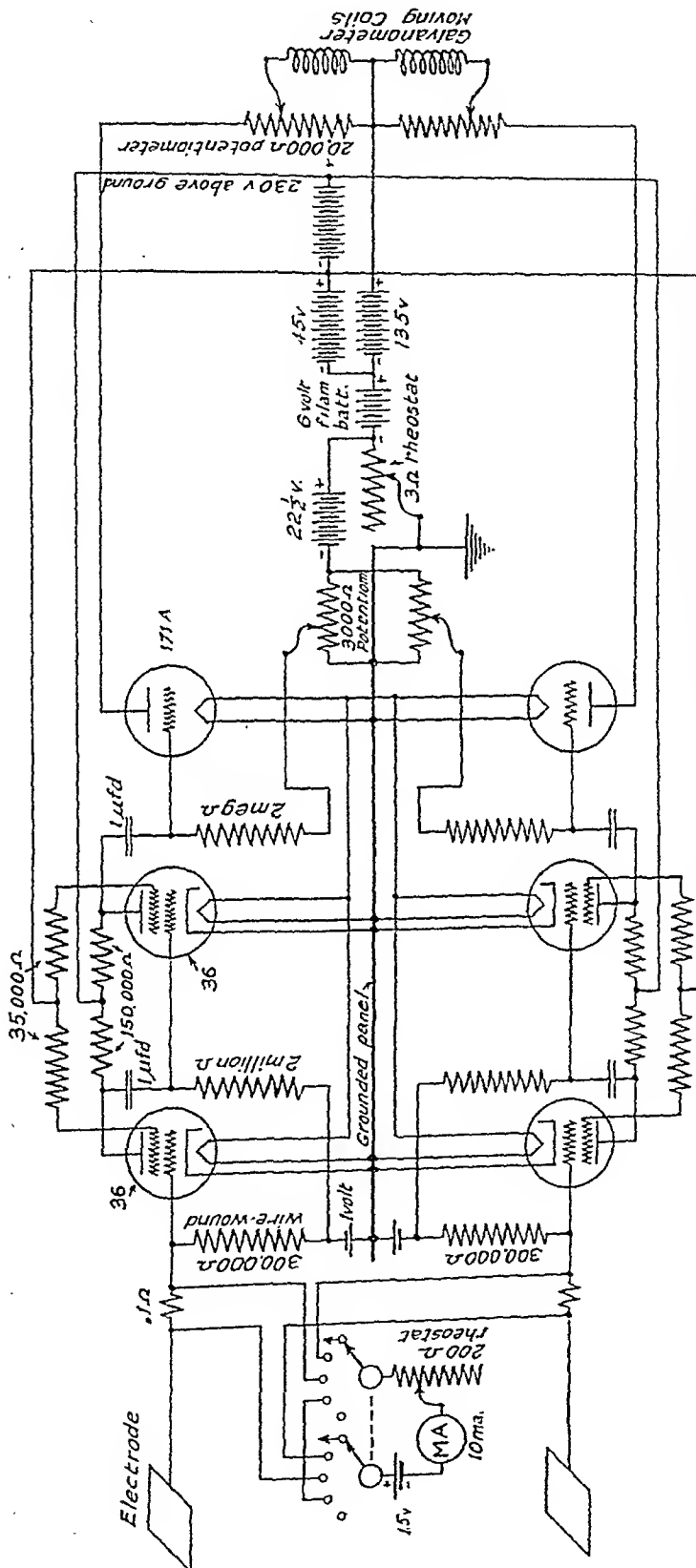


Fig. 1.—Diagram of the electrical circuit of the monocardiograph. The diagram shows two three-stage amplifiers arranged symmetrically with respect to the grounded panel. In actual practice three such amplifiers are arranged symmetrically. The connections of the third amplifier, which is not shown in the drawing, are exactly the same as the connections of the two amplifiers shown. The three sets of amplifiers are all operated by the same batteries as shown in the illustration.

galvanometric value. The coupling circuits between the tubes (1-microfarad condensers and 2-megohm grid leaks) are designed to pass the slowest T-waves. The amplifiers can easily pass the fastest impulses the heart produces.

The negative potential on the grids of the three power tubes can be adjusted by three independent 3,000-ohm potentiometers. This changes the amount of steady current delivered by the tubes to the galvanometer without much changing the amplification. This operation is useful in adjusting the zero point of the galvanometer.

The gain from each amplifier can be attenuated at the galvanometer by three 20,000-ohm potentiometers. By adjusting these potentiometers the amount of amplification can be varied within wide limits (about 1,000 per cent), and the three amplifiers can be made exactly equal to each other.

The complete amplifier with its nine tubes, resistances, condensers, grid-bias cells, and control panel is mounted in a metal box which rests on an air cushion so that it is unaffected by external vibrations. The batteries for the filaments and the plates are located separately and connected to the amplifier by shielded cables.

For standardization, a separate box is provided, containing a dry cell, a rheostat to control current from the cell, a milliammeter to indicate that current, and a double-bank switch to switch that current to each of three equal resistors made of

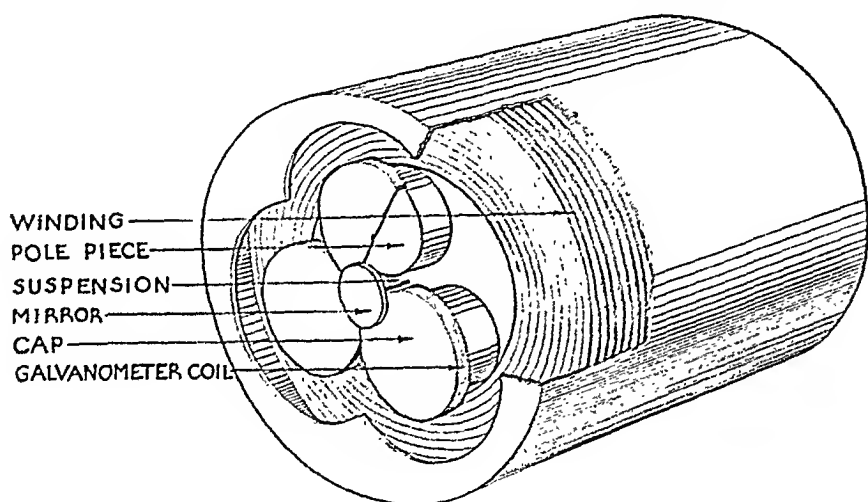


Fig. 2.—Diagrammatic representation of the special galvanometer used in the monocardlograph. The galvanometer coils are wound around the edges of the three caps, which are arranged in clover-leaf form. The curved mirror is rigidly attached to these three caps, which are fastened together and held in position by a suspension, which is merely a short straight wire. The caps are slightly larger than the pole pieces so that they can move without touching them. The field winding of the magnet is shown.

manganin alloy. These manganin resistors have a value (about 0.1 ohm) such that when the milliammeter reads 10 milliamperes there will be a voltage across them of 1 mv. (1 mv. = 1 R). The three resistors are connected in series with the patient leads as shown in the diagram (Fig. 1). When the current from the dry cell is adjusted by means of the rheostat to the standard value and the switch is turned, 1 mv. is applied to each of the amplifiers in succession. Thus each three-stage amplifier can be tested independently of the other two.

2. The *galvanometer* (Fig. 2) was designed especially for the monocardlograph. The moving part consists of a cluster of three movable coils, rigidly fastened together in one plane and pivoted universally at the center of gravity of the group. The framework of this system consists of three small, very light, duralumin caps, grouped like a clover leaf. The coils are wound around the edges of the caps. They consist of 1,500 turns of 0.001 inch insulated copper wire. The resistance of each coil is about 1,200 ohms. Very fine flexible leads are brought from these coils to fixed terminals.

The moving system is entirely supported by a very short bronze wire which is located at the center of gravity to minimize transfer of external vibrations. As each coil pulls or pushes in response to current fluctuations, the whole system tilts about its center of suspension. This it can do in any direction. The three coils are suspended in the air gap of a powerful electromagnet which has a three-knobbed pole piece, one knob projecting inside each cap. It is the reaction between the magnetic flux from this electromagnet, passing radially through the sides of the caps and the coils, and the current in the coils, which produces the motion. This same magnetic flux generates currents in the caps and coils when they are in motion which damp their tendency to vibrate and to overshoot. Air trapped inside the caps by the close fitting (but not touching) pole knobs also contributes to this damping. The result is that in spite of the weight and speed of the movable system it does not overshoot at all. A full deflection, approximately, can be obtained in 0.013 second. When used in connection with the amplifier and the optical system here described, this galvanometer can register a deflection of as much as 4 em. per millivolt of current obtained from the patient. The whole galvanometer, which weighs about five pounds, is loosely hung in a rubber sling.

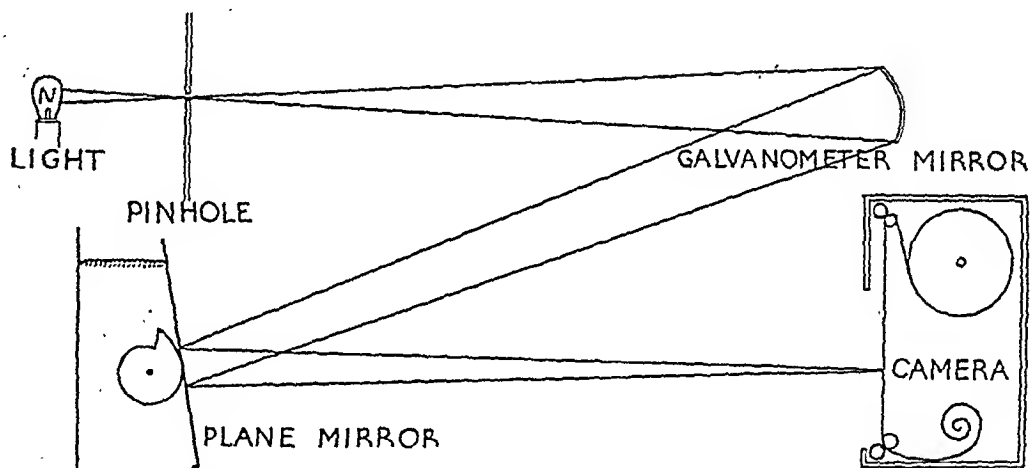


Fig. 3.—Diagrammatic scheme of the optical system of the monocardigraph. The light illuminates a pinhole, the image of which is reflected by the galvanometer mirror to a plane mirror and thence to the camera. The plane mirror is caused to oscillate by a cam in such a way that the image of the pinhole on the camera moves at the same speed as the sensitive paper.

3. The optical system (Fig. 3) is distinguished by its simplicity. No lenses are used, and only two reflecting surfaces are interposed between the lamp and the camera. The lamp, an ordinary concentrated filament lamp of 100-watt rating, illuminates a hole about 0.3 mm. in diameter, placed as near the lamp as possible. Through this tiny hole the light beam from a portion of the filament is directed upon the galvanometer mirror. This mirror, $\frac{5}{16}$ inch in diameter and $\frac{1}{32}$ inch thick, is concave, and aluminized on its front surface. It projects an image of the pinhole on a moving photosensitive surface. This projected image is about 0.5 mm. in diameter and is bright enough to give good photographic records. Greater brightness can be obtained by using an arc lamp, but this is not ordinarily necessary.

Before reaching the photographic paper (or film), the beam of light from the galvanometer is reflected from a plane mirror also aluminized on its front surface. This plane mirror is caused to oscillate by a very accurate spiral step cam. The cam, driven by the same shaft which drives the camera, swings the plane mirror through a small angle at a constant rate, so that the spot of light on the photographic paper moves with the paper, and at exactly the same rate, for about 1 cm. Then

a strong spring causes the mirror to snap back to its starting point in about 0.001 second, and the spot again follows the movement of the paper. Although the paper in the camera moves continuously, it is as if it were moved along by periodic jerks 1 cm. in length and lasting 0.001 sec., with a stationary period between jerks. The recording is done during the stationary period. In effect, the duration of the stationary periods is varied only by varying the speed of the motor.

4. The camera (Fig. 3) is of the continuous motion type. The sensitive paper, or film, is 6 cm. wide and 200 feet long. It passes over a series of rollers which move it at a uniform speed. During this motion it is exposed to the light beam described above and then is passed into a storage receptacle from which it is eventually removed for ordinary photographic development. The camera rollers are driven by a shaft actuated by a motor of adjustable speed. The speed of the motor is regulated by a rheostat.

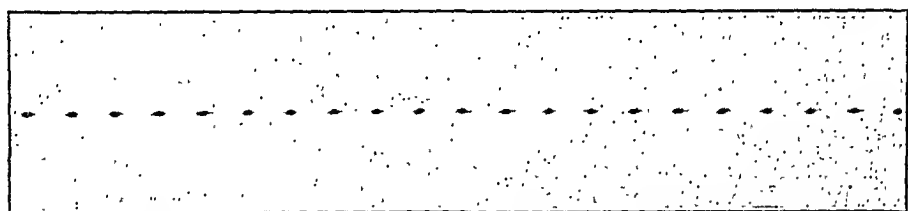


Fig. 4.—Record produced by monocardigraph when no patient is connected.



Fig. 5.—Record of standardization.

The operation of the monocardigraph is somewhat similar to the operation of an electrocardiograph. Electrodes are applied in the customary fashion to the two arms and the left leg. These electrodes are connected by a shielded cable to the amplifier. After turning on the amplifier, the lamp, and the galvanometer, the spot of light is centered on the camera by means of the potentiometers, and the amplification is adjusted to the desired degree. The standardization of each lead is tested and recorded on the first part of the film, after which the camera is allowed to run until a sufficient number of beats has been recorded.

Development and fixing of the photographic record follow.

SUMMARY

From the foregoing description it is evident that this instrument produces a curve by means described in 1929¹ as a "reversal of the process by which three leads are derived from one heart." The three leads are first amplified; they are then synthesized into one single curve; and finally this curve is recorded photographically.

MONOCARDIOGRAMS

For a clear understanding of the records produced by the monocardigraph it is advisable first to consider the record inscribed when the instrument is run without being connected to a patient. Fig. 4 shows such a record, a series of small sharp spots spaced about 1 cm. apart; it is to be read from left to right. This spacing is produced by the oscillating mirror previously described and is necessary for proper separation of consecutive waves. If a stationary spot of light were focused on the continuously moving sensitive paper, the result would be a continuous line, and any curves which might be produced would be distorted by the continuous movement of the tracing beam. The optical system used in the monocardigraph overcomes this difficulty by keeping the beam focused on one point of the moving paper for a definite period of time and then suddenly shifting the beam to a new center 1 cm. removed. Thus we obtain a series of frames similar to the separate frames of a motion-picture film.

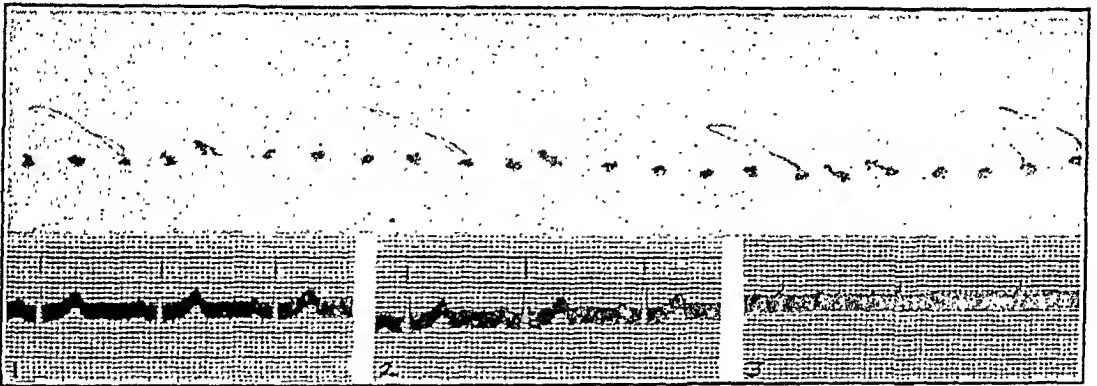


Fig. 6.—Normal monocardigram. The electrocardiogram of the same patient is shown.

Fig. 5 shows a record of the standardization of the three leads, obtained by introducing a standardizing current of 1 mv. into each of the three sets of amplifiers. The galvanometer deflections occur in three directions separated by angles of 120 degrees, or, in other words, in a way which corresponds to the three sides of an equilateral triangle. It can be seen that the galvanometer does not overshoot and that it is dead-beat.

Fig. 6 illustrates the succession of events when a patient with a fairly normal heart is connected. This record, reading from left to right, consists of a succession of small spots, or frames, and in addition there occurs at regular intervals a series of curves or waves, as follows:

(1) An auricular wave which corresponds to the P-wave of the electrocardiogram. This wave is generally small and ill-defined with the amplification here used. In records of patients whose electrocardiograms show large P-waves, the monocardigram shows distinct auricular waves.

(2) A large, smooth curve which represents the major electrical activity of the ventricles, and corresponds to the QRS-wave of the electrocardiogram.

(3) A rather small wave which represents the terminal ventricular activity, and corresponds to the T-wave of the electrocardiogram.

When the patient exhibits muscle tremor or slight movements of the large muscles, the smaller waves of the monocardigram are obscured, and only the main ventricular deflection is recorded clearly. Because of its magnitude and the ease with which it is recorded, this main complex is most accessible for preliminary study. Most of our observations will center around this part of the monocardigram.

The relationship between the main deflection in the monocardigram and in the three leads of the standard electrocardiogram is illustrated in Fig. 7. This figure shows the monocardigrams of two patients, each surrounded by the three leads of the corresponding electrocardiogram, properly arranged on the sides of Einthoven's triangle. The first mono-

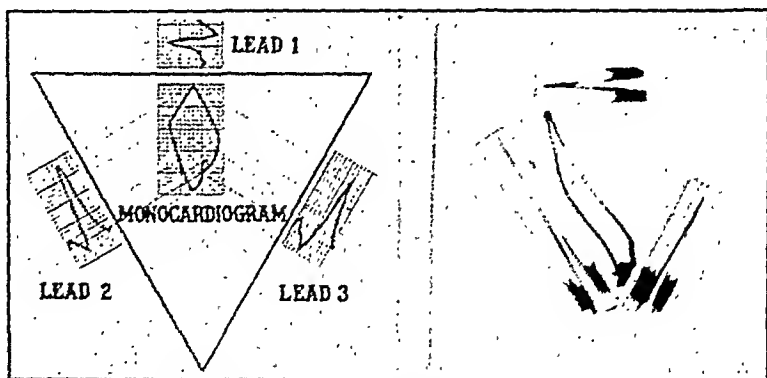


Fig. 7.—Relationship of monocardigram and electrocardiogram shown graphically by means of Einthoven's triangle.

cardiogram was not recorded instrumentally, but was derived mathematically and geometrically from three simultaneous leads of an electrocardiogram originally published by Einthoven.² The second monocardigram was recorded directly by connecting the patient to the monocardigraph. It can be seen that in each instance the central curve or monocardigram represents a combination or fusion of the three leads into a single polar curve, or that, conversely, the three standard leads represent projections of the monocardigram upon the sides of Einthoven's triangle. Every monocardigram can be similarly arranged inside Einthoven's triangle with the leads of the corresponding electrocardiogram arranged on the three sides of the triangle.

It is to be noted that the monocardigram does not have time lines such as are customarily recorded on the standard electrocardiogram. The monocardigram, being a polar curve, uses both the horizontal and vertical dimensions to indicate voltage. Because of this it has a directional significance which is obscured in the ordinary electrocardiogram,

in which the horizontal axis is devoted to time indication and only the vertical axis can indicate voltage. The ordinary electrocardiogram is especially well-suited to the recording of cardiac arrhythmias and curves in which measurement of the time element is important. The monocardium, on the other hand, is not well-suited for time measurements, but is especially adapted to measurements of spatial relations, such as changes in the cardiac axis, location of site of origin of extrasystoles, localization of myocardial impairment, etc. This will become clearer upon study of the curves which follow.

Nevertheless, there are in the monocardium certain indications of time relationships which will repay study. With the camera running at any constant speed the spacing of the various waves will give a fair idea of their temporal sequence. In studying a single wave one should remember that the darker or heavier parts of the curve represent the slower movements of the galvanometer, and that, when the galvanometer

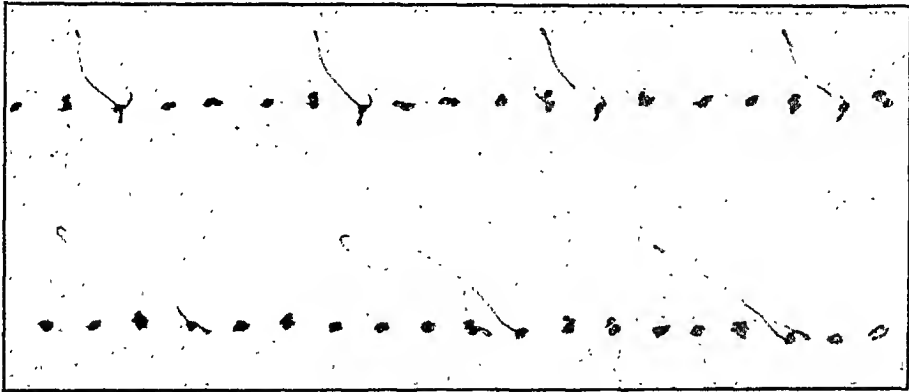


Fig. 8.—Normal monocardiums.

moves more rapidly, the resulting line is thinner and fainter. But there is one temporal relationship not recorded by the electrocardiograph which is brought out clearly in the monocardium. This is indicated by the direction in which the main deflection is traced. The main deflection, being in most cases a closed curve, might obviously be traced in one of two ways, namely, either clockwise or counterclockwise. Either method of tracing would produce the same curve, for the beginning and the end of the curve are in the same spot. It will be noted that in some of the records the tracing beam has shifted to a new center or frame when the curve has been only partly traced. This produces a peculiar effect due to the fact that part of the curve is in one frame and the remainder in the following frame. Obviously the part of the curve which is traced first appears in the first frame and the later part of the curve appears in the later frame. This division of the curve into two successive parts gives information about which part of the curve is traced first, and thus shows whether the curve was traced in a clockwise or counterclockwise direction.

Not all curves can be so interpreted. Some curves of peculiar shape are partly clockwise and partly counterclockwise. It is difficult to follow the direction of S-shaped curves and very narrow loops, but the clockwise or counterclockwise course of the vast majority of monocardigrams can be traced very easily.

The monocardigrams of two patients whose electrocardiograms are fairly normal are reproduced in Fig. 8. Each record shows a main deflection which has been recorded in two frames, and it can be seen that the curves are traced in a clockwise direction. Both records show main

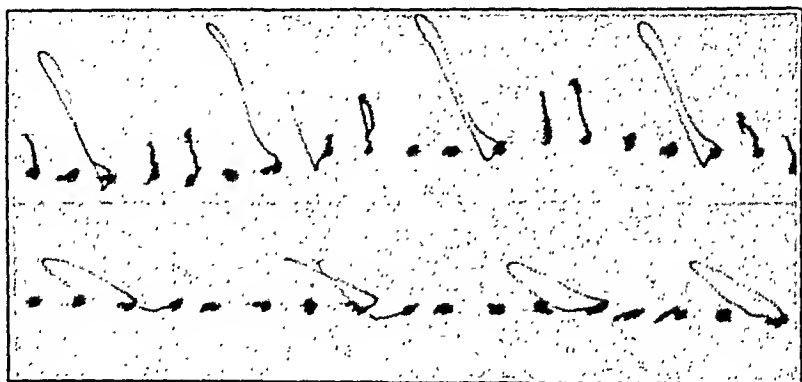


Fig. 9.—Upper curve shows prominent T-wave. Lower curve shows counterclockwise direction of the main deflection.

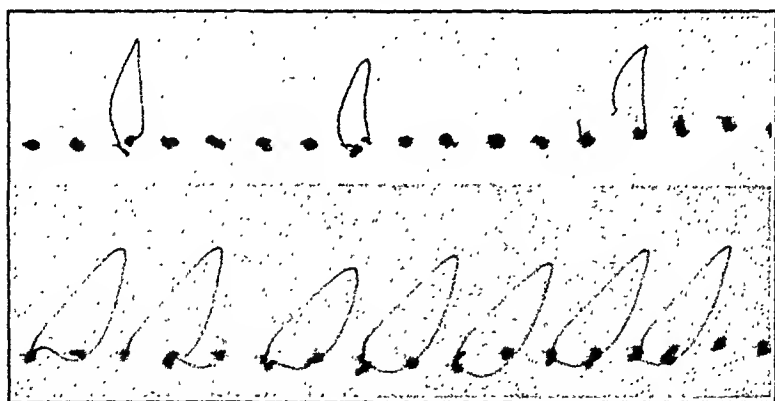


Fig. 10.—Right ventricular predominance.

deflections which are directed upward and to the left of the zero point or central spot, thus corresponding to a main deflection which is upright in Leads I and II of the electrocardiogram. The main deflection in the monocardigram is a fairly smooth, rounded curve, without sharp breaks or irregularities. The standardization of these and succeeding curves is roughly twice normal, i.e., 1 mv. produces a deflection of about 2 cm. In spite of this, the P- and T-deflections are small.

Fig. 9 shows the monocardigram of a patient with prominent T-waves. The second monocardigram is of interest because of the fact that the main deflection is traced in a counterclockwise direction.

Fig. 10 shows the monocardigram of a patient in whose electrocardiogram the R-wave was very low in Lead I and that of a patient with frank right ventricular predominance (this patient also has auricular fibrillation). In right ventricular predominance the main deflection of the monocardigram is directed upward and to the right, corresponding to an inversion of the main deflection in Lead I of the electrocardiogram.

With left ventricular predominance the main deflection of the monocardigram is directed to the left and downward, corresponding to inversion of the main deflection in Lead III of the electrocardiogram. Fig. 11 illustrates this, as well as the fact that most monocardigrams showing left ventricular predominance are traced counterclockwise, in contrast to the clockwise direction of most curves with no predominance or right predominance.

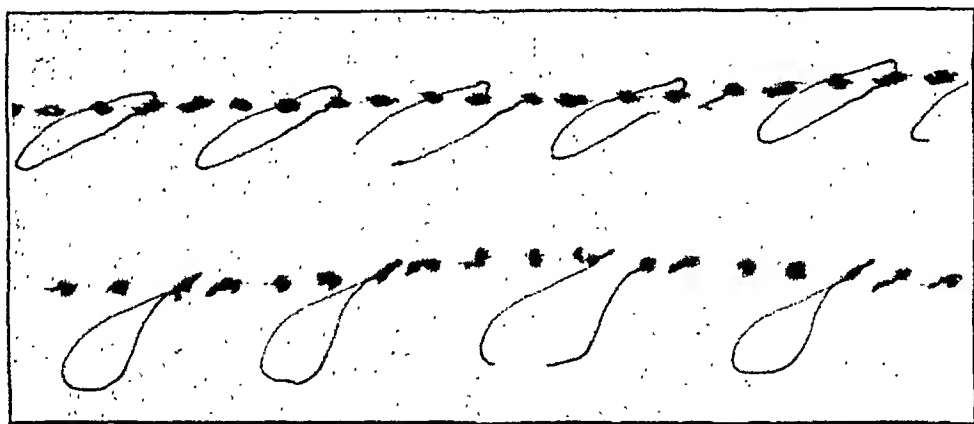


Fig. 11.—Left ventricular predominance.

Figs. 8, 9, 10, and 11, when examined with respect to the direction in which the curve points, indicate the cause for inversions of the main deflection in the electrocardiogram. When the monocardigram points upward and to the observer's right, as in Fig. 10, it is evident that a projection of this curve upon Einthoven's triangle will produce an inverted main deflection in Lead I, as in right ventricular predominance. When the monocardigram points upward and to the observer's left, as in Fig. 9, Leads I and II of the electrocardiogram will be upright, and the main deflection in Lead III may vary from the upright position to slight inversion. When the monocardigram points downward and to the observer's left, as in Fig. 11, the electrocardiogram must show definite inversion of the main deflection in Lead III, as in left ventricular predominance.

The direction in which the monocardigram points can be changed by forced respiration while a record is being taken, and this respiratory change affords a method of observing and measuring the respiratory mobility of the heart.

Fig. 12 shows two monocardio-grams in which the main deflection does not fall into the simple classification previously given. The electrocardiograms of these patients are likewise anomalous.

Thus far, all of the monocardio-grams shown have had main deflections of fairly smooth contour. The smooth contour suggests a smooth or regular spreading of the excitation wave through the ventricles such as normally occurs with an intact conduction system. Impairment of the intraventricular conduction system or interference with the normal mechanism of ventricular excitation may be expected to produce definite changes in the monocardio-gram. On a priori grounds we would

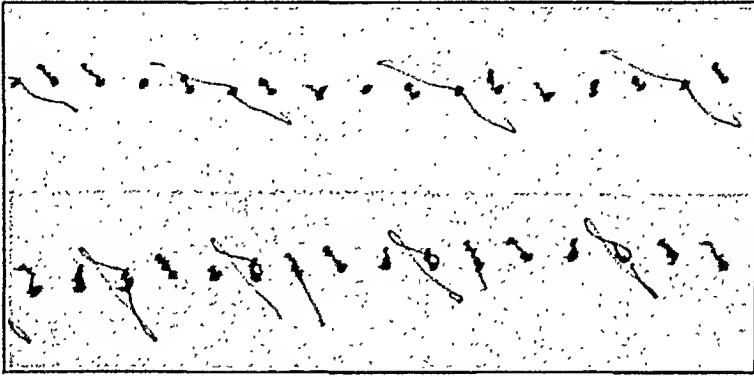


Fig. 12.—Mixed predominance.

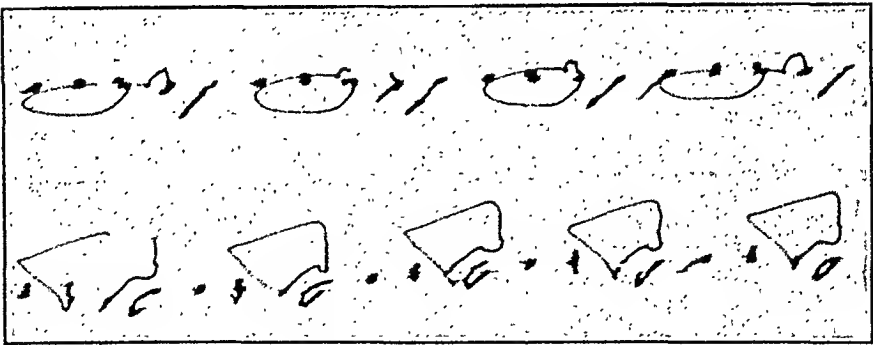


Fig. 13.—Intraventricular conduction defects.

assume that, when the spread of intraventricular excitation is seriously impaired, the main deflection of the monocardio-gram will show evidences of abnormality, such as peculiar or irregular contours. In actual records such evidences of abnormality are commonly encountered in the monocardio-grams of patients with intraventricular conduction defects. Not only do the main deflections in the monocardio-gram assume peculiar and bizarre shapes, but the normally smooth curve is often replaced by one of irregular, notched or eroded contour. The curves which follow illustrate conditions in which there is impairment or disturbance in the normal mechanism of ventricular excitation.

Fig. 13 illustrates this irregularity of the main deflection. The first curve shows a main deflection which is fairly normal in contour through-

out most of its course, but is suddenly interrupted in its terminal portion by an irregular arc which is not a smooth continuation of the previous curve. This first curve also shows left ventricular predominance and a prominent T-deflection which is inverted in Leads II and III of the electrocardiogram. The second curve shows a main deflection, the terminal third of which is distinctly irregular. Here again the T-waves are abnormal.

The great variety of curves which correspond to intraventricular conduction defects is illustrated in Fig. 14. Here it is evident that those curves which in the electrocardiogram are ascribed to "arborization block" present in the monocardiogram a variety of abnormalities which will provide a separate field for study, classification, and interpretation.

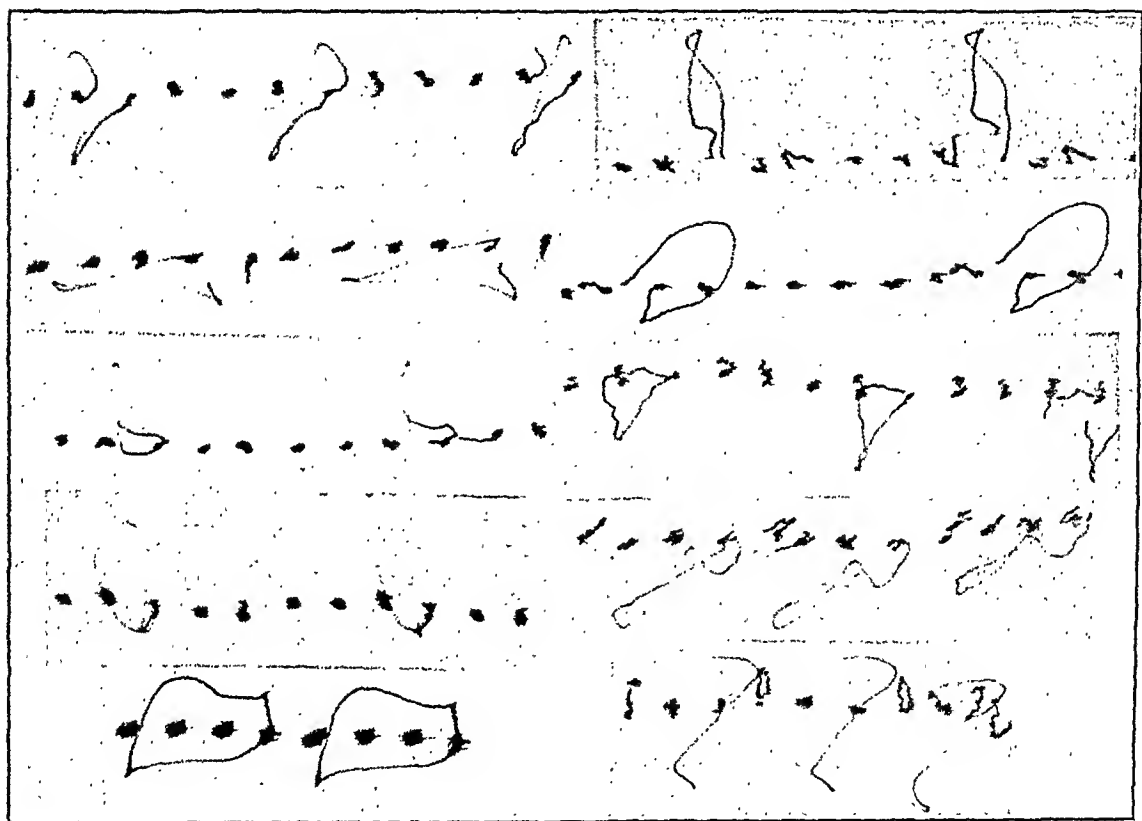


Fig. 14.—Curves showing a variety of intraventricular conduction defects.

Bundle branch block produces characteristic changes in the monocardiogram. In Fig. 15A* the main deflection is directed downward and to the observer's left, which direction is the result of left bundle branch block, and in Fig. 15B the main deflection is directed upward and to the right, indicating right bundle branch block. The patient whose monocardiogram is reproduced in Fig. 15B had a congenital septal defect. Roentgenkymograms made by Dr. Seth Hirsh gave evidence of a definite delay in the contraction of the right ventricle.

Acute coronary artery disease, as opposed to chronic myocardial damage, is known to produce gross changes in the R-T transition and in the T-waves of the electrocardiogram. The monocardiogram shows

*The courtesy of Dr. Ernst P. Boas made it possible to obtain this record.

these changes in a characteristic way. Fig. 13 shows abnormal T-waves. In normal monocardioagrams the T-deflection points upward and to the observer's left, as does the main deflection. A T-deflection which points to the right indicates an inverted T-wave in Lead I of the electrocardiogram. A T-deflection which points horizontally to the left, or downward, corresponds to inversion in Leads II and III of the electrocardiogram.

In Fig. 16A, from a case of coronary occlusion, the T-wave points to the observer's right. The main deflection fails to return to the central (isoelectric) spot, indicating an abnormal take-off of the T-wave. Fig.

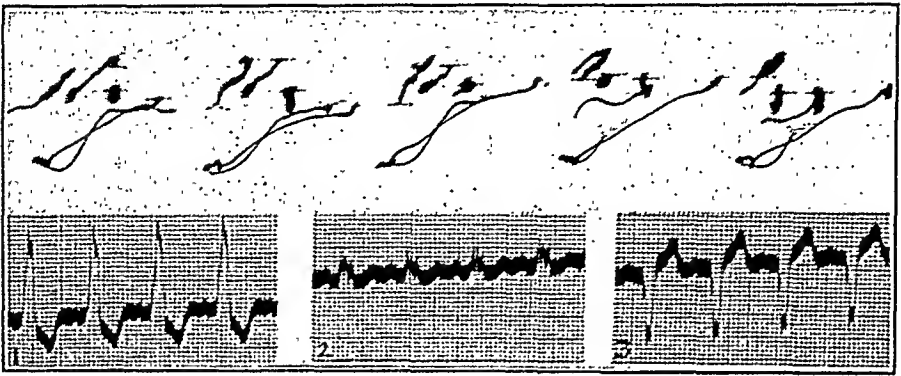


Fig. 15A.—Left bundle branch block.

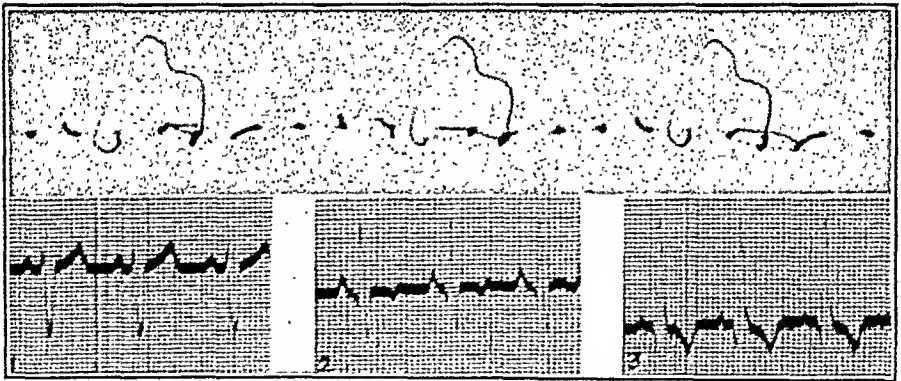


Fig. 15B.—Right bundle branch block.

16B shows a T-wave which is directed downward and to the left, indicating inversion of this deflection in Leads II and III. In both of these curves the main deflections show evidences of abnormality.

Extrasystoles provide a fertile field for monocardiographic study. The direction in which the extrasystole points gives evidence of its origin; one should always bear in mind that Einthoven's triangle is so drawn that the right side is to the observer's left, and vice versa. In Fig. 17 the first curve illustrates an extrasystole which apparently arises in the region of the right apex. The second curve shows an extrasystole which seems to arise at the left base. Fig. 18 illustrates the bizarre forms which extrasystoles sometimes assume.

In the following discussion of the significance and uses of the monocardio-gram, the author has made use of several hundred monocardio-grams taken during the past six years. The curves reproduced in this

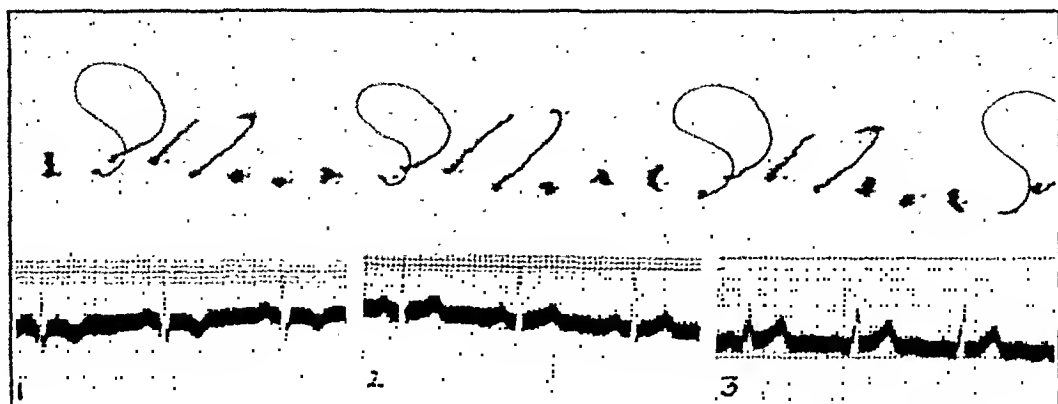


Fig. 16A.—Abnormal T-wave of the type generally associated with anterior coronary closure.

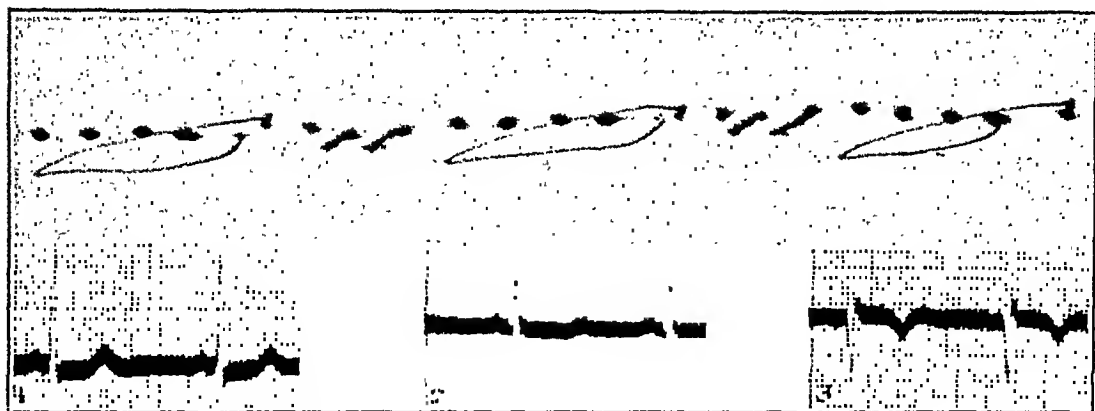


Fig. 16B.—Abnormal T-wave of the type generally associated with posterior coronary closure.

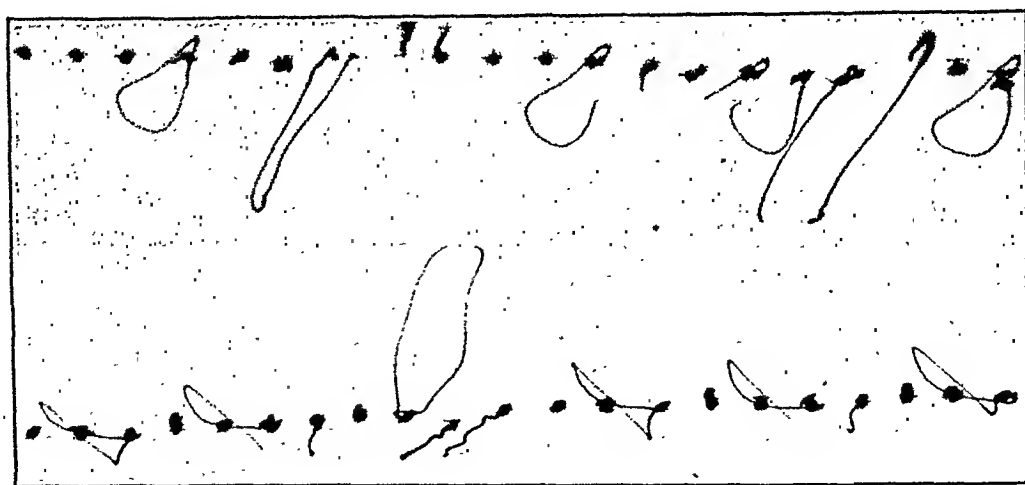


Fig. 17.—Ventricular extrasystoles interrupting sinus rhythm.

article, although limited in number, will serve to illustrate many of the points here considered.

Very early in the work evidence began to accumulate as to the directional significance of the monocardio-gram. About 1926, when the monocardio-gram in its crude form consisted of a cathode-ray oscillograph

with two amplifiers but with no permanent recording device, an opportunity was presented for testing the directional significance of the curves. A patient who had had part of the left chest wall removed some years previously was the subject. In this patient the precordium was covered only by fibrous tissue and skin, so that it was easy to produce extrasystoles by tapping lightly over the precordium. It was not possible to say with certainty which ventricle was being stimulated, but one could be reasonably certain whether he was tapping near the base of the heart or near the apex. The monocardio-grams of these extrasystoles were upright when the base of the heart was tapped, inverted when the apex was tapped, and intermediate in form for intermediate points. Even before this it had become evident from direct observation that hearts of different shapes and sizes gave quite different curves and that right and left ventricular predominance produced characteristic changes in the direction of the main deflection. Forced respiration fre-



Fig. 18.—Bizarre type of ventricular extrasystoles.

quently produced rotation of the monocardio-gram corresponding to the known direction of anatomical rotation.

These observations have been confirmed and extended by a study of the recorded curves, so that it is now possible to say with reasonable assurance that the monocardio-gram, as recorded, has a directional significance which is only obscurely revealed by the electrocardiogram. The monocardio-gram has sacrificed the time axis of the electrocardiogram and is therefore unable to delineate the arrhythmias, but in doing this it has gained a second space axis, so that it is able to record spatial and directional relations which have hitherto been obscure. In the curves which show these spatial and directional relations, extrasystoles stand out as prominent and relatively simple examples. The monocardio-gram, as recorded, gives valuable evidence as to the site of origin of ventricular extrasystoles, and a classification of such extrasystoles according to the direction and shape of their monocardio-grams should be of value.

There are many less spectacular spatial and directional features of the monocardigram which should reward the investigator. The significance of clockwise or counterclockwise tracing of the various waves is obscure, but may be significant, and will probably repay careful study. Ventricular predominance produces obvious changes in the monocardigram, and, if great accuracy is desired, the direction in which the monocardigram points can be indicated by degrees. Right and left bundle branch block produce characteristic monocardigrams in which the activity of the intact ventricle obviously precedes that of the other.

Myocardial and coronary disease are interesting fields for monocardigraphic study. As we have seen, monocardigrams of "arborization block" reveal abnormalities of certain parts of the main deflection. A study of these abnormalities may give valuable information, and the location of the lesion in coronary artery disease may be ascertained with considerable precision. By taking monocardigrams from three points in a frontal plane, instead of the usual sagittal plane, further information about anterior and posterior lesions may become available.

Auricular flutter and fibrillation suggest further uses for the monocardigram. With increased amplification and suitable patients, it is not unreasonable to expect that we may be able to investigate the circus movement of flutter and possibly discover its location. The irregular circus movement of auricular fibrillation may yield records of interest and value.

SUMMARY

After a discussion of the principles underlying the monocardigraph, and a brief history of the evolution of this instrument, a detailed description of the instrument follows. The nature of the curves obtained by means of the monocardigraph is explained, and examples are given of monocardigrams characteristic of normal hearts and those which show ventricular predominance, "arborization block," bundle branch block, coronary artery disease, and extrasystoles.

The author wishes to express his thanks and appreciation to John F. Pattee for his indispensable assistance in designing and constructing many of the parts of the monocardigraph, and to Dorothy Rolph for her drawings.

The construction of the monocardigraph was aided by a grant from the Rockefeller Institute, to which the author wishes to express his appreciation.

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THE PRECORDIAL ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION*†‡

I. OBSERVATIONS ON CASES WITH INFARCTION PRINCIPALLY OF THE ANTERIOR WALL OF THE LEFT VENTRICLE AND ADJACENT SEPTUM

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THIS paper is the first of a series dealing with the potential variations of six precordial points, and of the right arm, left arm, and left leg, in cases of myocardial infarction. Our work was an outgrowth of the detailed experiments of Wilson, Hill, and Johnston,¹ who have demonstrated^{1, 2} that the chief difference between precordial and direct leads is quantitative and that human precordial electrocardiograms are comparable to experimental direct leads in dogs. Between the two, however, there are several important differences which will be pointed out later. In this work we have adopted the method introduced by Wilson and his associates⁴ and used by Wilson³ in his study of 60 cases of myocardial infarction.

Our series comprises 127 cases of myocardial infarction. Of the 22 patients known to have died, 17 were subjected to post-mortem examination. Because an analysis of the necropsy observations is necessary for a proper understanding of the many cardiac factors which influence the precordial electrocardiogram, these observations have been divided into several groups. The first group, with which this paper is concerned, includes 4 cases of infarction principally of the anterior wall of the left ventricle, in 3 of which the anterior portion of the interventricular septum was also involved.

METHODS

In each case the standard leads were recorded first. The potential variations of the right arm (V_R), the left arm (V_L), the left leg (V_F), and of six precordial points were then obtained by pairing an exploring electrode with a central terminal connected to the right arm, the left arm, and the left leg, through resistances of 5,000 ohms each. This method has been shown to yield curves which represent the potential variations of the exploring electrode; the central terminal remains at zero potential throughout the cardiac cycle.⁴ The following precordial points were explored: the fifth rib at the right sternal edge (V_1); the fifth rib at the left sternal

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edge (V_2); the fifth intercostal space in the left parasternal line (V_2); the fifth intercostal space in the left midclavicular line (V_4); the sixth rib in the left anterior axillary line (V_6); and the tip of the ensiform cartilage (V_R). In taking the extremity and precordial potentials the connections to the galvanometer were so arranged that a downward movement in the finished record represented positivity of the exploring electrode.*

The galvanometer was a Hindle No. 2, made by the Cambridge Instrument Co., and the string resistance was 4,000 ohms. The string was connected to the balanced plate circuit of a single-stage vacuum tube amplifier. Standard leads and extremity potentials (V_R , V_L , V_F) were taken at normal, precordial potentials at half-normal (1 cm. = 2 mv.), sensitivity of the string. The exploring electrode was a piece of sponge moistened with saturated salt solution, which made contact in the lower end of an ordinary glass test tube with a German silver plate.

At necropsy, the heart was opened in the usual way by following the path of the circulation. Macroscopic observations having been made and recorded, the specimen was fixed in Kniserling I solution for a variable period, usually longer than twenty-four hours. Photographs were taken when indicated, and the heart was then sutured together again. At this stage the coronary arteries were examined by making transverse incisions $\frac{1}{2}$ cm. apart down to the smallest visible branches. In every specimen an attempt was made to identify and study the following vessels: the left coronary artery and its branches, i.e., ramus descendens anterior and its accessory branches, ramus circumflexus, rami marginis obtusae, rami ventriculi sinistri posteriores, and the ramus descendens posterior (when present); the right circumflex coronary artery and its branches, i.e., rami anteriores, ramus lateralis (margo acutis), ramus ventriculi dextri posterior, ramus descendens posterior, and the rami ventriculi sinistri posteriores. Needless to say, the course, particularly of the descending rami, and the number and size of rami of the main branches, showed some variations. The coronary arterial system of each heart was drawn diagrammatically to scale with the lesions observed represented in code (Fig. 3 and legend). In every instance arterial abnormalities seen with the naked eye were checked microscopically. Even if no obvious change was encountered, sections were taken for microscopic study from the left and right coronary arteries, the ramus circumflexus, the ramus descendens anterior, and the ramus descendens posterior. Macroscopic abnormalities noted in the coronary veins were similarly dealt with.

The sutured heart was then placed in a rotary slicing machine and cut into transverse sections approximately 1 cm. in thickness. The usual yield was six sections, although the number varied from five to eight, depending on the size of the heart. A basal section, approximately 3 to 5 cm. in thickness, which included the aortic and pulmonary valves and the roots of the great vessels, remained. This was cut with a knife into multiple sections so that no recent or old infarcts might be overlooked. The basal (proximal) surface of each section was photographed in such a way that in the finished picture the anterior wall was below, and the left ventricle to the right (Figs. 2, 5, 8, 10).

Blocks for histologic study were cut from all diseased areas, as well as from representative portions of each ventricle and from the interventricular septum, regardless of the appearance to the naked eye. In every case at least one micro-

*The records were therefore taken and the letters Q, R, and S assigned to the initial ventricular deflections as in the paper by Kossmann and Johnston,⁶ which deals with the curves obtained by means of the same special leads in a series of normal subjects. It has been recommended by the Committee on Precordial Leads of the American Heart Association that the galvanometer connections be made in the opposite way, so that positivity of the exploring electrode will be represented by an upward, instead of a downward, deflection. Since the letters Q, R, and S have been assigned as if the curves were reversed, the individual QRS deflections in our figures bear the names recommended by the committee. An initial summit is Q, a depression is R, and a summit preceded by a depression is S. With this nomenclature the RS or intrinsicoid deflection⁶ is analagous to the intrinsic deflection⁷ of direct leads.

scopic section of the aorta and one section of the auricular muscle were made. Duplicate sections were stained with hematoxylin and eosin and with a combined van Gieson-Weigert elastic tissue stain. A few were stained for fat with sudan III.

In Case 2, the relationship of each of the precordial heaving-off points to the heart was ascertained by introducing a blunt probe perpendicular to the chest wall before the autopsy was performed. Figs. 5 and 6 show where the probe pierced the heart.

REPORT OF CASES

CASE 1.—C. A., a man 66 years old, first noted symptoms of diminished cardiac reserve in January, 1935, following an upper respiratory infection, and on April 13, 1935, he had symptoms of coronary occlusion. When he was admitted to the hospital



Fig. 1.—Case 1. Photograph of heart looking into the cavity of the left ventricle. The anterior wall is to the left. Old thrombus can be seen adherent to the interventricular septum, anterior wall, and entire apex. Scarring and thinning of the underlying myocardium are visible. Thickened endocardium shows as an irregular white line.

April 20, 1935, he had moderate congestive heart failure with pronounced mental symptoms, e.g., lethargy, dullness, disorientation, and memory defects. The heart was slightly enlarged, and the sounds were distant. There was a systolic murmur at the apex and another in the aortic area. The precordium seemed to be tender to pressure. The heart was beating regularly 100 times a minute. The blood pressure was 140/100. The mean blood pressure over a period of a month (daily measurements) was 138/90. A blood Wassermann test was negative.

The heart failure was progressive. Beginning April 23, the patient was digitalized rapidly and thereafter given 3 grains (2 cat units) daily. Fluids were administered parenterally, and the blood nonprotein nitrogen, which was 60 mg. per cent on admission, fell to 32 mg. per cent, but the patient developed decubitus

ulcers and Cheyne-Stokes respiration, and died of pulmonary edema May 25, 1935, five months after the first symptoms of heart disease, and forty-two days after the onset of symptoms of coronary occlusion.

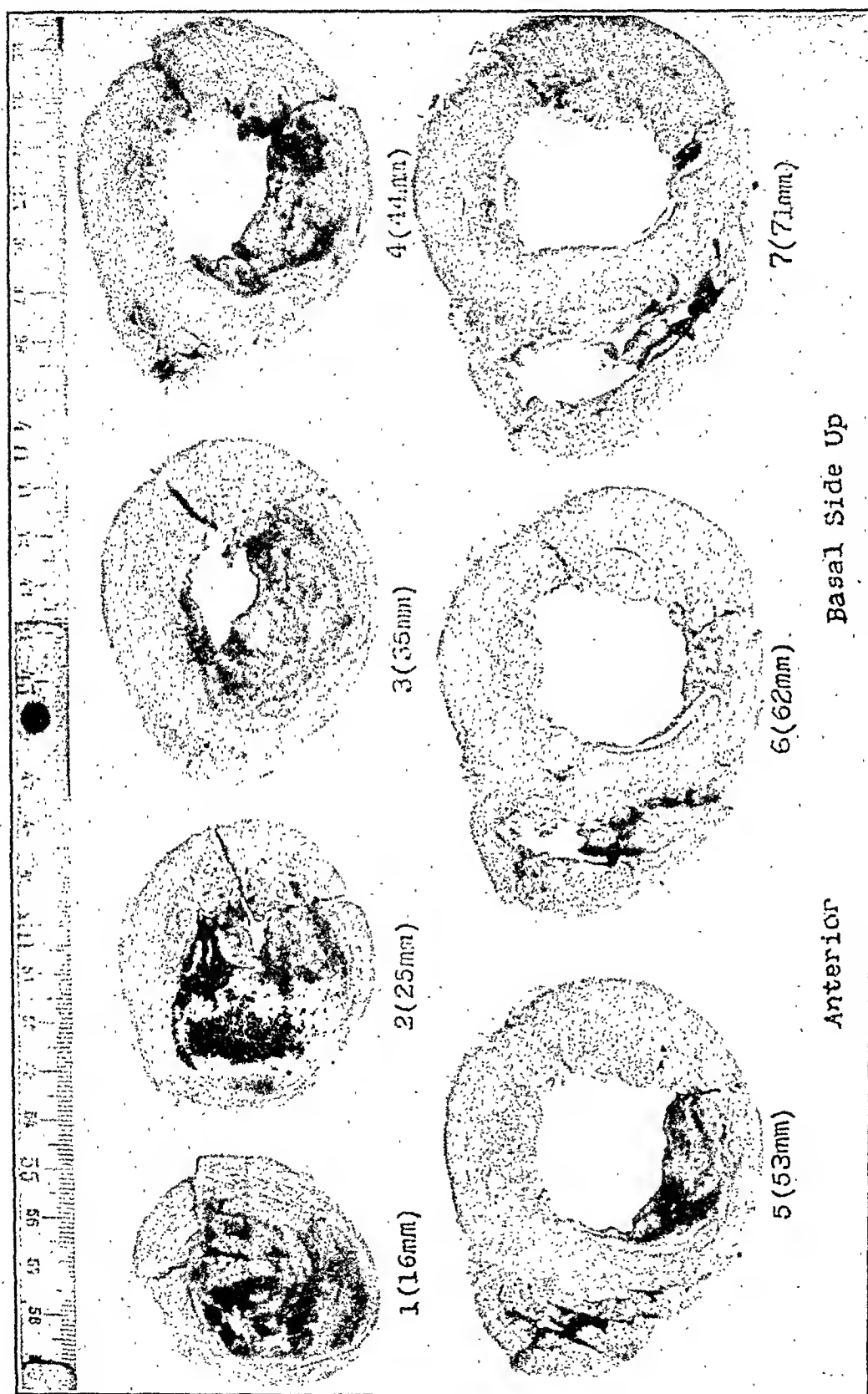


Fig. 2.—Same heart as in Fig. 1 (Case 1) cut into transverse sections, which are numbered consecutively from apex to base. The basal side of each section has been photographed with the anterior wall below, with the exception of section 1, which is rotated slightly in a counterclockwise direction. The number in parentheses under each section indicates its distance in millimeters from the apex of the heart. The intraventricular thrombus is dark in color and fills the apical sections. Note limitation, both of the thrombus and of the scarring, to the anterior wall of the left ventricle and adjacent septum, as the base is approached. Thickened endocardium can be seen as an irregular white line between the scarred myocardium and the intraventricular thrombus.

Necropsy.—The heart weighed 490 grams. The pericardial surfaces were smooth except near the apex, where there was an area of fibrinous exudate measuring 3 cm. × 3 cm. The valves of the heart and all of its chambers, except the enlarged left ventricle, were normal. The myocardium of the lower two-thirds of the anterior

portion of the interventricular septum and the apical one-third of the anterior left ventricular wall was replaced by firm, grayish-white tissue measuring about 4 to 6 mm. in thickness and located approximately 5 mm. subjacent to the epicardium. The endocardium of this area was thickened and covered with a large, firmly adherent, grayish-red thrombus of irregular outline (Figs. 1 and 2).

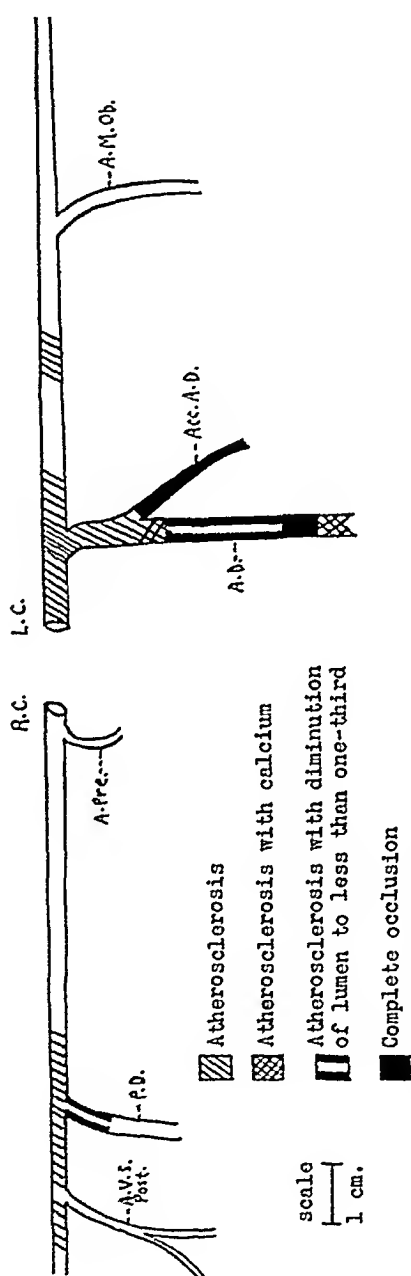


Fig. 3.—Case 1.—Coronary arteries. L. C., left coronary artery; A. D., ramus descendens anterior; Acc. A. D., accessory ramus descendens anterior; A. M. Ob., ramus marginis obtusae; R. C., right coronary artery; A. Prc., ramus anterior (pre-ventricular); P. D., ramus descendens posterior; A. V. S. Post., ramus ventriculi sinistri posterior. Lesions are indicated by the code in the lower left-hand corner.

In the transverse sections (Fig. 2) the myocardial infarct extended 7 cm. proximally from the apex. Its circumferential extent varied from 10 cm. in the apical section (Fig. 2, section 1) to 5 cm. at a level 62 mm. (Fig. 2, section 6) from the apex. In the two apical sections the infarct involved almost the entire thickness of the anterior and lateral walls of the left ventricle, only 1 to 1.5 mm. of subepicardial muscle remaining. In the more proximal sections the area of infarction was confined to the anterior wall of the left ventricle and to the left side of the anterior portion of the interventricular septum (Fig. 2, sections 5, 6, and 7).

Endocardial sclerosis was prominent over those portions of the left ventricle involved by the infarct. The right ventricle was unchanged.

Histologic examination of tissue removed from the transverse sections verified the macroscopic findings. Most of the infarct in the left ventricle was healed. In its peripheral portions organization was still in progress.

Macroscopic examination of the coronary vessels revealed marked atherosclerotic changes of the right and left coronary arteries and their branches (Fig. 3).

Microscopic examination indicated that the occlusion of the ramus descendens anterior 3 cm. from its origin was due either to eccentric intimal hyperplasia or to an organized thrombus. In its accessory branch a recent thrombus occluded the greatly narrowed lumen. The ramus descendens anterior was obviously the vessel of supply in the infarcted area.



Fig. 4.—Standard electrocardiograms (I, II, III), extremity potentials (V_R , V_L , V_F), and precordial potentials (V_1 , V_2 , V_3 , V_4 , V_5 , V_6) in Case 1, taken seventeen days after the onset of symptoms typical of coronary occlusion. The patient was completely digitalized. The standard leads and extremity potentials were recorded with the string at normal sensitivity; the precordial potentials were recorded at half-normal sensitivity (1 cm. = 2 mv.). An upward deflection in the special electrocardiograms represents relative negativity of the exploring electrode. Initial ventricular deflections are named, therefore, in a reverse manner (see footnote on p. 701). Time lines occur every 0.2 sec.

Unless otherwise stated, the symbols, string sensitivity, connections to galvanometer, and time lines are the same in all subsequent electrocardiographic illustrations.

Electrocardiograms.—Nine standard electrocardiograms were obtained, all of which showed sinus rhythm, low amplitude of both the initial and final ventricular deflections, and inversion of T_3 . Curves taken after April 23 showed some depression of RS-T in Leads I and II, but this was probably due to digitalis and was not great, as comparison with the curve taken before the institution of therapy showed.

Precordial and extremity potentials were recorded on April 30, 1935, seventeen days after the probable date of coronary occlusion, seven days after digitalis was begun, and twenty-five days before

death. These are shown with the standard leads obtained on that date in Fig. 4. The extremity potentials, V_R , V_L , V_F , are of low amplitude. Also, as would be expected from the degree of left axis deviation shown in the standard leads, the potential of the left arm is positive and that of the left leg negative during the inscription of the initial ventricular deflections.

The precordial potentials (V_1 , V_2 , V_3 , V_4 , V_5 , V_6) are distinctly abnormal. All of the initial ventricular deflections begin with a negative wave, Q. In Leads V_4 and V_5 this is small and not definitely outside normal limits. From points on the right side of the precordium (V_1 , V_2 , V_3) it is the only QRS deflection. In Lead V_2 it is followed by a small positive deflection, R. The final ventricular deflections are abnormal in the leads from the right side of the precordium, but little significance can be attached to this abnormality because the patient was completely digitalized.

CASE 2.—J. McE., a white male vagabond 54 years of age, had eaten irregularly for a year. There were no indications of heart disease until Feb. 8, 1936, when at 1:00 P.M. symptoms typical of coronary occlusion became manifest. He was admitted to the hospital February 9. The principal physical findings were malnutrition, enlargement of the heart, and marked sclerosis of the peripheral vessels. The heart was beating regularly at a rate of 88 per minute. On admission, the blood pressure was 128/88, and the mean of seven blood pressure readings was 136/89.

A teleoroentgenogram made on February 18 showed enlargement of the heart and sclerosis of the aorta. The erythrocyte count was 2,330,000, and the hemoglobin 58 per cent (Dare). A blood Wassermann test was negative.

Signs of congestive heart failure, which were absent on admission, developed rapidly with the patient at rest in bed. Digitalis, first administered February 18, produced only slight and temporary improvement. Shortly before death, icterus, hypothermia, and signs of cerebral anoxemia developed. Death occurred on February 23 from congestive heart failure, fifteen days after the onset of symptoms of coronary occlusion.

Necropsy.—The heart weighed 480 gm. The pericardium was normal. All of the valves and chambers were normal except the left ventricle, which was moderately dilated and hypertrophied, measuring 16 mm. in thickness at the base. Its anterior wall and the adjacent anterior portion of the interventricular septum were mottled in appearance, and distinctly softer and thinner than the rest of the myocardium. The columnae carneae were flattened. The infarct extended from a level 2 cm. below the mitral ring to within a centimeter of the apex.

Examination of the transverse sections (Fig. 5) revealed that the area of softening and mottling (outlined by broken white lines in the figure) extended from the apical level to within a few centimeters of the base of the heart, 8 cm. in all. In the apical section (Fig. 5, section 1) it involved practically the entire circumference of the left ventricle. Proximally, the circumferential involvement diminished, i.e., to 8 cm. in section 3, 6 cm. in section 4, and 1 cm. in the basal section. In the apical sections the infarct was largely subendocardial, becoming more intramuscular at higher levels but not reaching the epicardium at any point. Sections 3, 4, 5, and 6 showed distinct thinning of the anterior part of the septum, and in the last section the adjacent anterior walls of both the right and left ventricles were considerably thinner than usual.

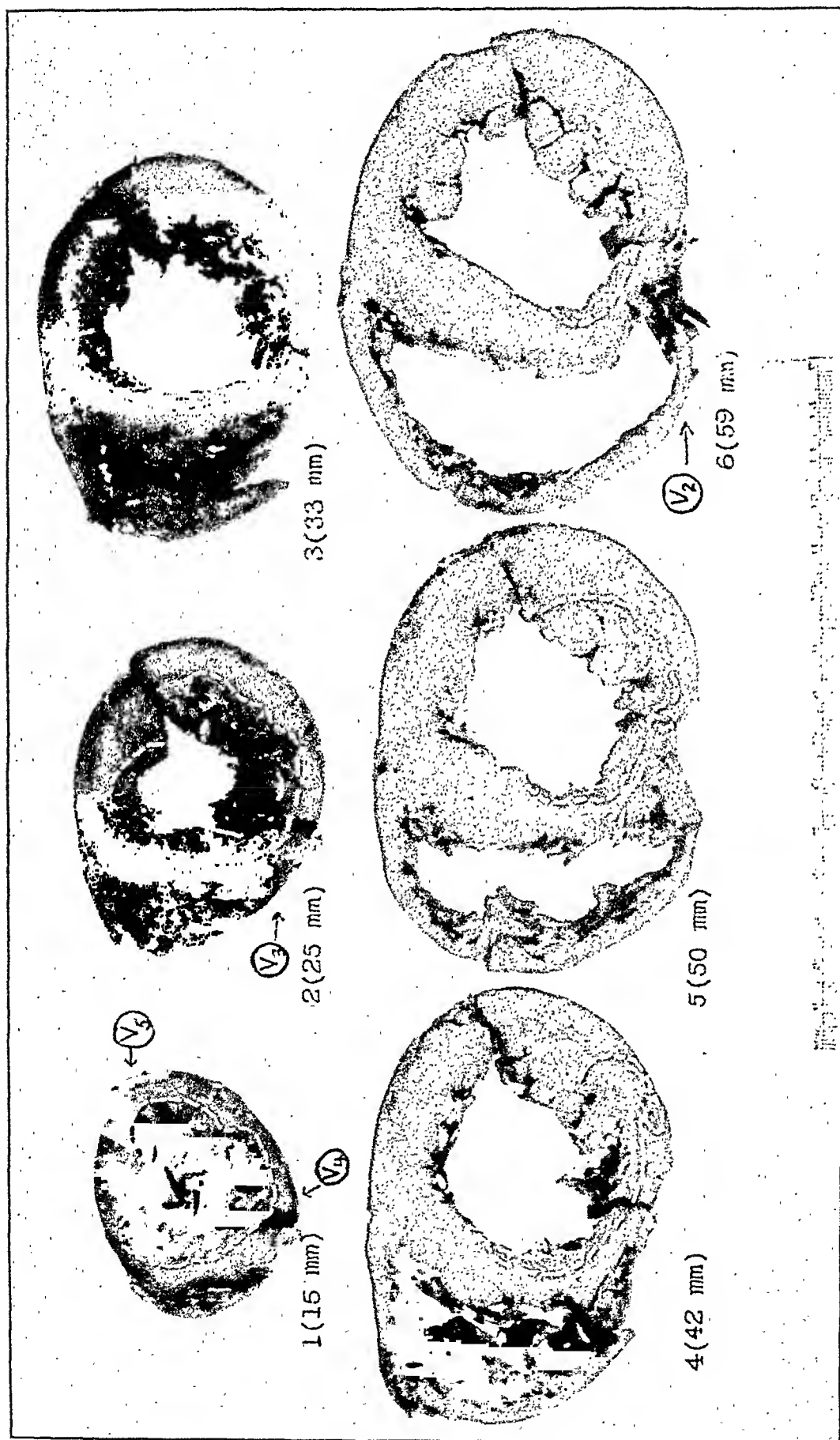


Fig. 5.—Case 2. Sections of the heart. The basal side of each section is seen, with the anterior wall below. The subendocardial extent of the infarct is outlined in white. The sections are numbered from apex to base. The figure in parentheses after each number indicates the distance in millimeters of that level from the apex. V_2 , V_3 , V_4 , and V_5 show where a probe pierced the heart when introduced perpendicular to the chest wall at the following precordial points: V_2 , the upper angle made by the junction of the fifth left rib with the sternum; V_3 , fifth intercostal space in the left parasternal line; V_4 , fifth intercostal space in the left midclavicular line; V_5 , upper border of the sixth rib in the left anterior axillary line.

Histologic examination of the transverse sections revealed a recent, organizing infarct involving the area described. A small mural thrombus was seen in an apical section. In all sections the epicardium was thickened, except over the posterior wall of the left ventricle and over the right ventricle, and consisted of widely separated collagen fibers; many injected vessels and diffuse lymphocytic infiltration were also present. In a section through the lateral wall of the left ventricle fibrin was present on the epicardium, and there were a few invading histiocytes, but the infarcted area did not extend to the epicardium.

The area not involved by the infarct contained scattered foci of interfascicular and interstitial fibrosis. There were numerous arterioles which showed considerable reduplication of the internal elastic layer.

Gross and microscopic examination of the coronary arteries (Fig. 6) revealed severe atherosclerosis. The ramus descendens anterior of the left coronary artery

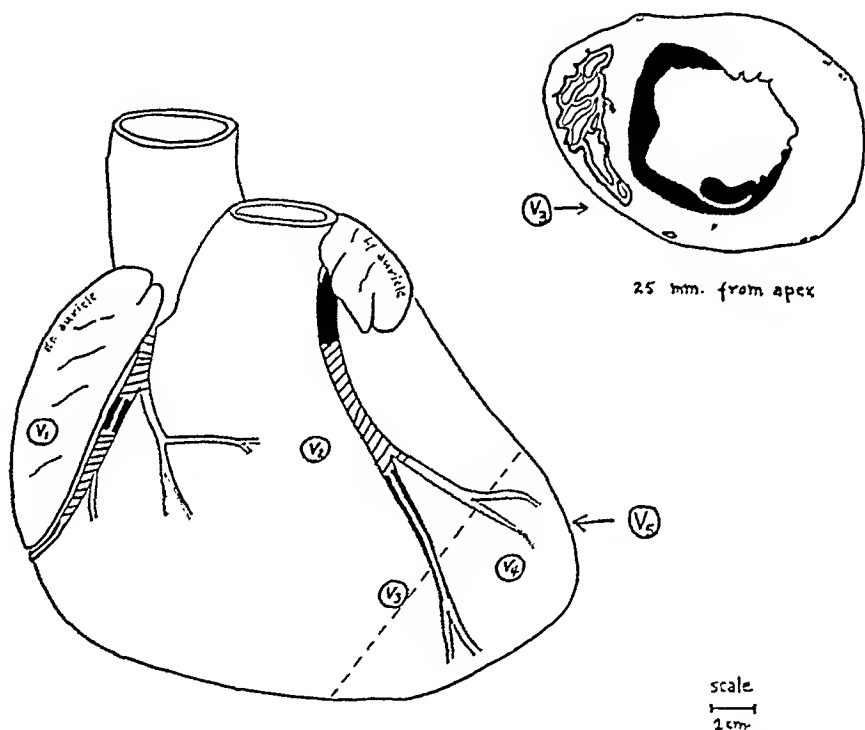


Fig. 6.—Diagrammatic representation of heart and coronary arteries in Case 2. Lesions in the arteries are indicated by the code used in Fig 3. V_1 , V_2 , V_3 , V_4 , and V_5 indicate where a probe which was pushed perpendicularly through the chest wall at the same precordial points from which Leads V_1 through V_5 were recorded (see Fig. 5) pierced the epicardium. When the probe was introduced at the ensiform process, it did not touch the heart. Inset in the upper right-hand corner is the section obtained by cutting through the dotted line shown near the apex. It corresponds to section 2 of Fig 5. The infarct is represented on it by solid black. The figure is intended to show particularly the spatial relationship to the heart of the precordial point used to record Lead V_3 (fifth intercostal space in the left parasternal line).

beginning at a point a few millimeters beyond its origin was occluded by a recent thrombus, 2 cm. long. The lumen of the right coronary artery was reduced in places to slitlike proportions.

Electrocardiograms.—Four standard electrocardiograms were taken between Feb. 10 and Feb. 22, 1936. All showed sinus rhythm and left axis deviation. The initial ventricular deflections were similar in all, exhibiting low amplitude with a small Q-wave, and a small slurred R-wave in Lead I; a prominent S-wave was present in Leads II and

III. The T-wave was inverted in Lead I in all curves, but in Leads II and III it varied a little, finally becoming upright as indicated in Fig. 7. The electrocardiograms, in short, showed a Q_1T_1 pattern, with a small Q_1 .

The extremity and precordial potentials (Fig. 7) were recorded on Feb. 22, fourteen days after the appearance of symptoms of coronary occlusion, and one day before death. In the preceding four days the patient had received 21 grains (13 cat units) of digitalis by mouth. A study (unpublished) which we have made on the effect of digitalis on precordial potentials leads us to think that this amount probably had little effect on the final ventricular deflections in this case. The

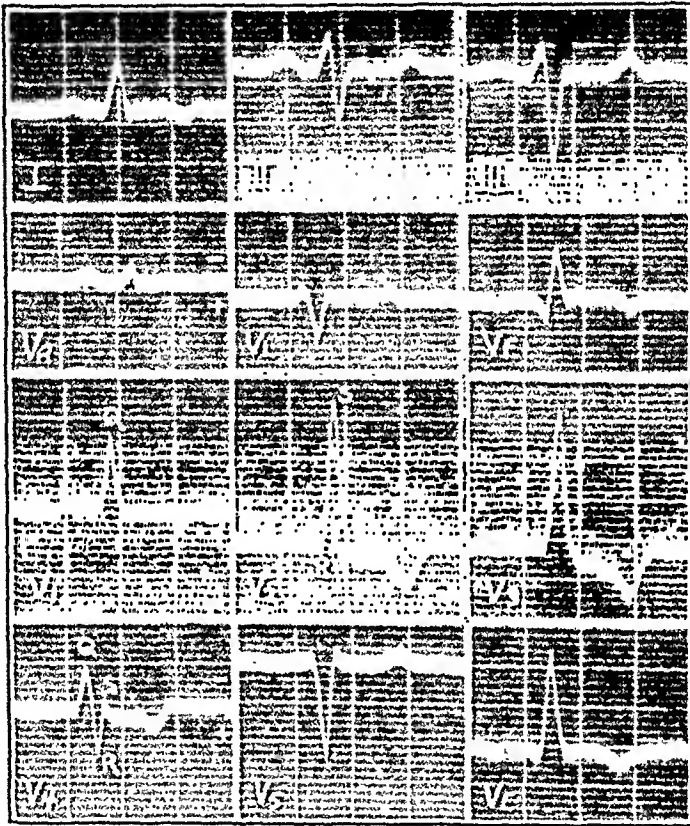


Fig. 7.—Case 2. Standard and special electrocardiograms recorded fourteen days after the occurrence of coronary occlusion.

minor changes in the T-waves in the standard leads following digitalis therapy support this belief.

The extremity potentials were of the type seen with left axis deviation. However, in contrast to Case 1, the potentials of the left arm and left leg showed small initial deflections opposite in direction to the chief deflection. Stated symbolically, V_L showed a small Q followed by a prominent R, and V_F showed a small R followed by a prominent S.

The precordial potentials were similar to those of Case 1 with the following differences: In Leads V_2 , V_3 , and V_E , there was a small initial positive deflection (R-wave); Lead V_4 was similar to Lead V_3 in Case 1, and both were similar to curves obtained experimentally¹

from the margin of a recent infarct; there was considerable positive displacement of RS-T in Leads V₂ and V₃, less in Lead V₄; in Lead V₅ the T-wave was negative (upright).

CASE 3.—J. M., a white man 41 years of age, was a chronic alcoholic who had been drinking steadily for four or five weeks. The patient's personal history was unreliable, but apparently he had had temporary edema of the face and feet in November, 1935.

He was drunk when he was admitted to the Bellevue Psychiatric Pavilion Jan. 10, 1936, and had edema of the ankles, enlargement of the liver, and evidence of peripheral neuritis. The edema was thought to be nutritional because he had hypoproteinemia, a low or inverted albumin-globulin ratio on various occasions, and a history of inadequate diet. After four days of rest and an adequate diet the edema disappeared, and the patient was allowed out of bed. On January 20 he was observed to have dyspnea and cyanosis, during which he complained of pain over the precordium and his blood pressure fell. He passed through several similar episodes in the next few days. Signs of congestive heart failure appeared, and on January 25 he was digitalized. During that day he expectorated blood. Several subsequent hemoptyses were interpreted as indicating pulmonary infarctions.

Four roentgenograms taken at different times showed enlargement of the heart, dilatation of the aorta, and bilateral pleural effusion. The pleurae were tapped on several occasions. A blood Wassermann test was negative.

Signs of heart failure persisted. The pleural effusions became purulent, and cultures of the fluid revealed streptococcus viridans. The patient died of congestive heart failure and chronic bilateral empyema May 27, 1936, four months after the onset of symptoms of myocardial infarction.

Necropsy.—The heart, which weighed 480 gm., was greatly dilated, especially the left auricle. The mitral orifice measured 11 cm. and its valves showed moderate, diffuse thickening. The chordae tendineae and papillary muscles were prominent. The endocardium of the left ventricle was smooth except at the junction of the anterior wall and the interventricular septum, where it was thickened and overlaid by a grayish-red, firmly adherent thrombus. A small area of endocardium over the apical portion of the posterior wall presented the same changes.

Examination of the transverse sections (Fig. 8) showed the endocardium as an irregular, broad, white band over the areas mentioned. Small patches of adherent thrombus were seen over these areas. In section 4 (30 to 40 mm. from the apex) the endocardium appeared as dense white tissue, 2 mm. in thickness, from which bands of similar tissue extended into the myocardium. The muscle thus delimited presented a yellowish-gray mottled appearance. This zone measured 3 × 4 mm. Similar but smaller areas were seen in the corresponding portions of proximal sections (Fig. 8, section 6).

Histologically, scarring of the endocardium, together with superimposed organizing mural thrombi, was seen, and there were several corresponding subendocardial foci of necrosis in the myocardium. Both walls contained dense, avascular, collagen scars, chiefly subendocardial, which represented healed infarcts. In one of the anterior wall scars two arterioles, occluded by canalized thrombi, were seen.

Macroscopic and histologic examination of the coronary arteries revealed mild focal atherosclerosis. At the origin of the ramus descendens posterior (of the right coronary artery) there was eccentric atherosclerosis which involved a few millimeters of its course and diminished its lumen by one-half. The left coronary artery

was thin-walled and patent, but its ramus descendens anterior showed in the first centimeter of its course a large, eccentric, yellowish-white plaque which narrowed the lumen considerably.*

Electrocardiograms.—Ten standard electrocardiograms, all showing sinus rhythm, were recorded at intervals of approximately ten days. Only the first, taken Jan. 24, 1936, was obtained before any digitalis had been given. Its deflections were of low amplitude in all leads, but displayed a Q_1T_1 pattern. All subsequent standard leads were similar to those shown in Fig. 9, which was taken February 18. The

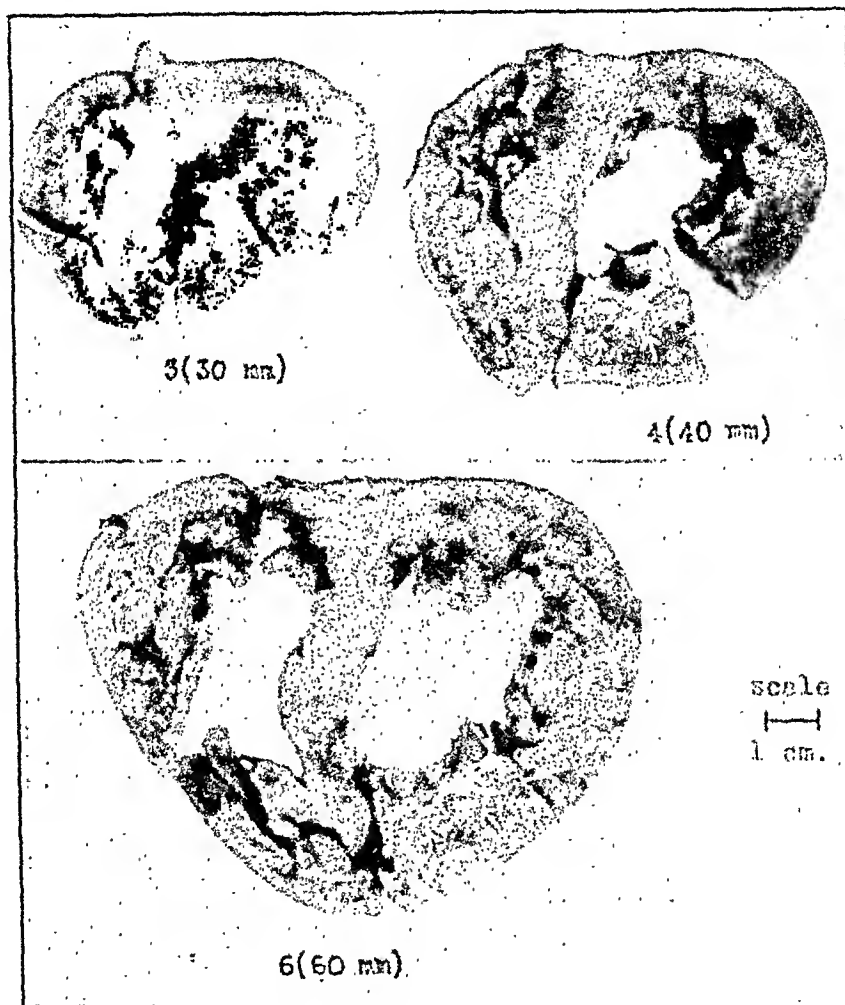


Fig. 8.—Sections of the heart in Case 3. Only three of the seven which were obtained are shown. Basal surfaces are seen with anterior wall below. The location of the thickened endocardium and the thin layer of subendocardial fibrosis are indicated by white arrows.

initial ventricular deflections were of abnormally small amplitude. In Lead III the chief, and usually the sole, initial deflection was downward, but in a few electrocardiograms this was preceded, and in one it was followed, by a small summit. The RS-T segment was slightly depressed in Leads I and II. The T-wave was low or isoelectric in all leads.

*The unusual features of this case were myocardial infarction without coronary occlusion, and bilateral empyema associated with multiple necrotic pulmonary infarcts. The latter has been discussed elsewhere.⁸

The extremity and precordial potentials were obtained twenty-nine days after the probable date of myocardial infarction. Although the amplitude of QRS was small in both, the relatively small size of the R-wave in leads from the first four precordial points was the striking feature. In Lead V₅, R was preceded by a small Q-wave.

The form of the initial ventricular deflections meant little because the patient was fully digitalized when the special curves were recorded.

CASE 4.—C. W., a man 76 years of age, had suffered since 1928 from post-prandial pain which radiated to the chest. May 24, 1936, he was awakened from

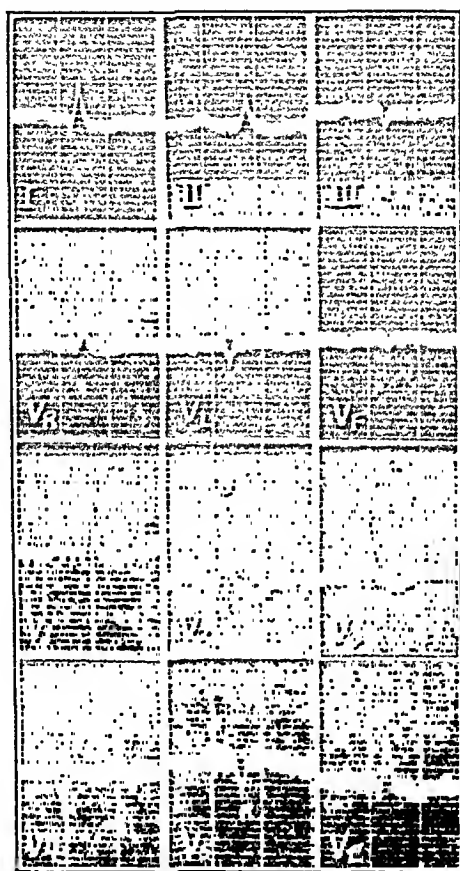


Fig. 9.—Case 3. Standard and special electrocardiograms recorded twenty-nine days after the probable date of myocardial infarction. The course oscillations in Leads V₁ and V₂ are artifacts. The patient was completely digitalized.

his sleep by symptoms which were suggestive of coronary occlusion. The next day, after the symptoms had abated, he entered the hospital. Roentgenologic examination showed that his heart was enlarged. The ventricular and pulse rates were 84 per minute. The blood pressure on the day of admission was 200/115, but fell five days later to 120/80, where it remained. There was no evidence of congestive heart failure. A blood Wassermann reaction was negative.

The patient's two months' stay in the hospital was uneventful except for brief precordial and epigastric pains radiating down the left arm on June 5 and again on June 12, 1936. On each occasion there was a leucocytosis and moderate rise in temperature.

The patient returned to the hospital Sept. 17, 1936, complaining of "epigastric distress" which disappeared after two weeks of rest in bed, and again Nov. 15, 1936, with symptoms and signs of congestive heart failure. Digitalis was given

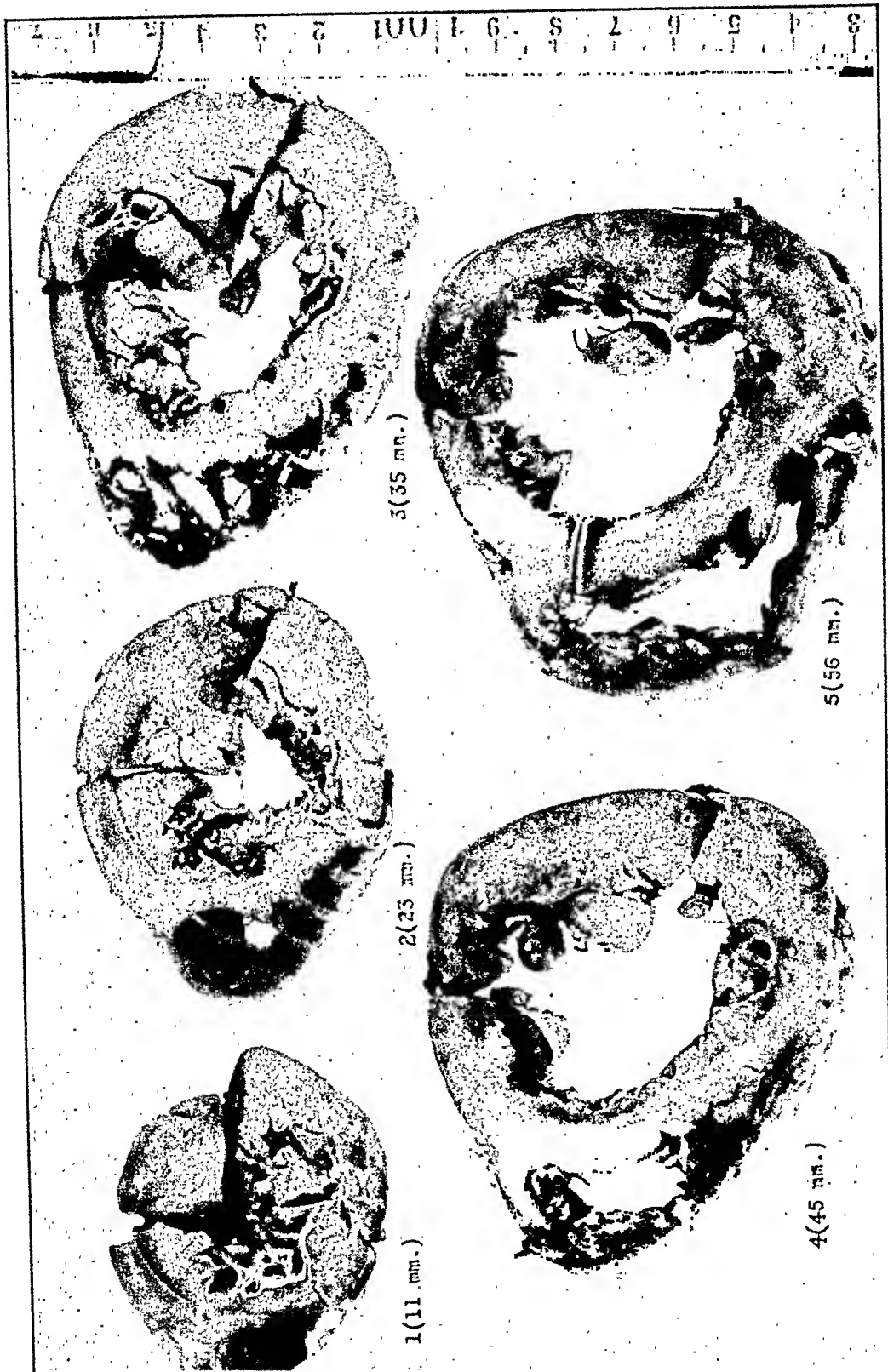


Fig. 10.—Sections of the heart in Case 1. In each, the basal side is up and the anterior wall is below. Note the pale, patchy scarring of the interventricular septum and adjacent anterior wall in all sections. In the first four sections thickening of the endocardium and an overlying adherent mural thrombus are visible. The transverse line over the posterior portion of the interventricular septum in section 5 is an artifact.

without benefit. Death occurred Nov. 28, 1936, five months after the first signs of coronary occlusion.

Necropsy.—The heart weighed 450 gm. The anterior wall of the left ventricle was the seat of many healed infarcts. Most of the midportion of the anterior three-fourths of the interventricular septum was replaced by a healed infarct (Fig.

10). Microscopically, healed lesions as well as recent subendocardial changes were found in the posterior wall of the left ventricle. The latter were seen only in the basal half of the heart, whereas the healed infarcts of the anterior wall and of the interventricular septum were found at all levels from apex to base (9 cm.). Organized mural thrombi were present in the anterior and septal walls of the left ventricle and in both auricles. The coronary arteries were sclerotic. The right coronary and ramus descendens of the left were almost completely occluded just beyond their origins. There was moderate narrowing throughout the entire extent of the circumflex branch of the left coronary artery. No recent or organized thrombi could be identified.

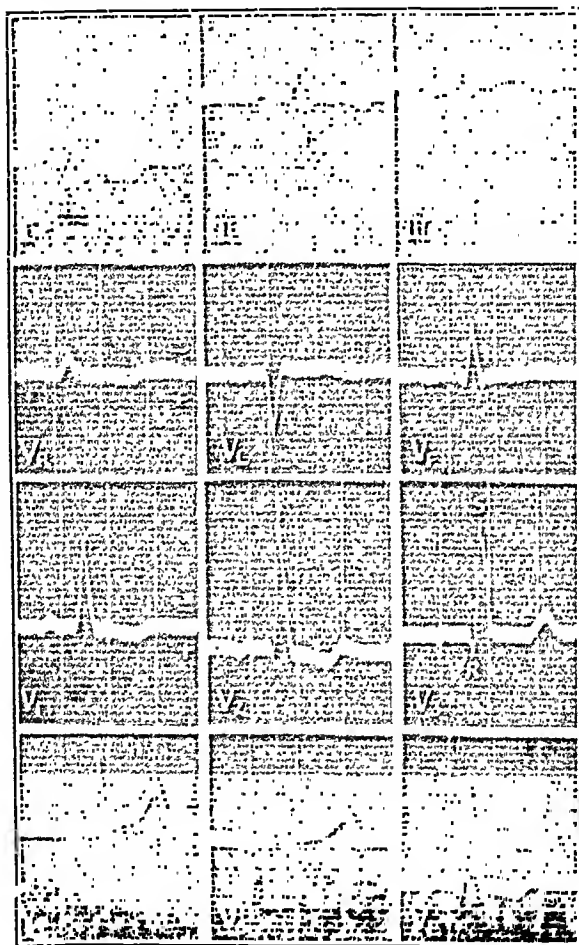


Fig. 11.—Case 4. Standard and special electrocardiograms recorded five days after the occurrence of coronary occlusion.

Electrocardiograms.—Twenty-four standard electrocardiograms, the first on May 25, 1936, were recorded during the three hospital admissions. All showed sinus rhythm and marked left axis deviation. In general, they were similar to the curve shown in Fig. 11, except that after the first electrocardiogram the amplitude of the initial ventricular deflections diminished. The QRS interval was 0.1 sec. in the curve shown in Fig. 11, but it increased later. During the last month of life, before any digitalis had been given, the P-R interval increased from about 0.16 or 0.17 sec. to 0.19 or 0.21 sec.

The extremity and precordial potentials were taken five days after the coronary occlusion and five months before death (Fig. 11). The potential of the left arm was positive, and of the left leg, negative, during the inscription of QRS. The precordial potentials were unusual. The R-wave was absent in Lead V_1 , which was abnormal. The R-wave in Leads V_2 , V_3 , and V_E were abnormally small, and the S-wave in Leads V_2 and V_3 abnormally large, as judged by the criteria of Kossmann and Johnston. The RS deflection in all leads was within normal limits, however. The negative displacement of RS-T in Lead V_4 , the negative T-wave in Leads V_3 , V_4 , and V_5 , and the diphasic T in Lead V_2 were abnormal.

DISCUSSION

The Precordial Leads.—The deviations of the precordial electrocardiogram from normal in experimental and clinical myocardial infarction have recently been summarized by Wilson.³ Experimental results in the early and late stages are quite constant, although acceptable explanations for some of the phenomena observed are lacking. The work of Wilson, Hill and Johnston¹ on dogs makes the following facts available: (1) Direct leads from infarcted areas which extend through the entire thickness of the ventricular wall yield curves which are characterized by a large initial negative deflection, Q, followed by a shallow, rounded, positive RS-T and T. Absence of the normal initial positive deflection (R-wave) is due to absence of electrical forces normally contributed by the involved muscle. For the sake of convenience this curve may be called the "central" type since it is obtained over the center of an infarct. (2) Curves obtained by direct leads from regions in which only the inner layers of muscle are infarcted may have a QRS group conforming to one of several patterns. It may consist of a single negative deflection, Q, with a prominent notch on its second limb. The notch may extend beyond the base line, in which event an R-wave and a true intrinsicoid⁶ or RS deflection is present. In curves of the latter type the final negative deflection is occasionally missing, leaving only Q and R. In areas yielding curves of these types the RS-T segment is usually flat, and the T-wave is negative and prominent. These changes in the final ventricular deflections are attributed to disturbances affecting the recovery process in damaged muscle at the margins of the infarct. They are seen during subacute stages of infarction and are temporary. These several varieties of curves may be called "marginal" types because they are obtained by leading from the margin of an infarct. (3) Electrocardiograms similar in form to those described are obtained when the exploring electrode is separated from the epicardial surface of the heart by a gauze pad wet with physiologic saline or by the tissues of the chest wall.

The precordial electrocardiograms in our first two cases are similar in many respects to the various experimental curves described by Wilson, Johnston, and Hill. In the first case (Fig. 4) Leads V_1 , V_2 , and V_E are similar to direct leads from the center, and Lead V_3 is similar to a direct lead from the margin, of an infarct. The latter consists of a large Q, a small R, and an intrinsicoid deflection which just returns to the base line, so that an S-wave is absent. The small Q-wave in Leads V_4 and V_5 is not quantitatively beyond normal limits.⁵ Digitalis probably had considerable effect upon the final ventricular deflections. However, it is to be noted that the position of the RS-T segment and the position of the apex of T are both reversed in Leads V_4 and V_5 as compared with Leads V_1 and V_2 .

In the second case (Fig. 7) Leads V_2 , V_3 , and V_E , which are of the "central" type, differ from those in the previous case in that they show a small R-wave. This deflection sometimes occurs in direct leads from the center of an infarct,¹ but its origin is not known. A "marginal" curve, in this instance with an S-wave, is seen in Lead V_4 . The abnormally positive RS-T segments in Leads V_2 and V_3 are in striking contrast to the relatively normal ones in the standard and extremity leads. The "marginal" curve (V_4) has a positive T, but its form is transitional between the relatively normal positive T in leads from points farther to the right and the abnormal T in Lead V_5 farther to the left.

An interesting observation in these two cases is that an infarct which was limited to the left side of the interventricular septum and to the anterior wall and apex of the left ventricle yielded chest leads of the "central" type, especially over the right side of the precordium. This, together with the fact that we had observed similar curves in a large number of cases diagnosed clinically as coronary occlusion, led us to perform the previously described probing experiment at necropsy in Case 2 in an effort to ascertain the anatomical relationship of the precordial points to the heart surface (Figs. 5 and 6). At the left sternal edge and in the left parasternal line (Leads V_2 and V_3) the probe entered the heart at the base and at the apex of the right ventricle, respectively; in the midclavicular line and in the anterior axillary line (Leads V_4 and V_5) it pierced the apex of the left ventricle; at the right sternal edge (Lead V_1) it entered the right auricle; and at the tip of the ensiform (Lead V_E) it did not touch the heart at all. Admitting that certain errors exist in such a procedure, it seems certain that the first three leads (V_1 , V_2 , V_3) were semidirect leads from areas of the heart surface to the right of the anterior interventricular groove.

The explanation for the "central" type of potentials in leads from the right half of the precordium in cases without infarction of the right ventricle is lacking, but, when this matter is considered in the

light of other observations, we suspect that such curves are due to the fact that infarction of the left side of the anterior interventricular septum has destroyed the electrical forces normally contributed by that side.

Whatever the correct explanation may be, the subject has considerable practical importance, for occasionally the R-wave is missing in Leads V_1 , V_2 , and V_E , and is small in midprecordial leads in cases with marked left ventricular hypertrophy.^{9, 10} The precordial potentials in cases of myocardial infarction can usually be differentiated from these by the similar absence of the R-wave in one or several of the remaining leads or by the presence of a "marginal" pattern in one of these leads; furthermore, in acute and subacute stages of anterior infarction the special electrocardiograms may frequently show an abnormal T-wave different from that seen in left ventricular hypertrophy.

The last part of this statement may be amplified by considering the chest leads in Case 4 (Fig. 11). The abnormalities of the initial ventricular deflections, including the absence of a true intrinsicoid or RS deflection in Lead V_1 , are not specific, for, as already noted, they are seen in cases of left ventricular hypertrophy. The weight of the heart was 450 gm., and hypertrophy of the left ventricle was moderate. It was doubtful, therefore, if these changes were independent of the infarct. The abnormal final ventricular deflections, on the other hand, are similar to those obtained after recent infarction of the anterior heart wall and are unlike those encountered in left ventricular enlargement. With the latter, a negative T-wave is found only in those curves obtained from precordial leads well to the left, where the R-wave is of considerable magnitude. In the case under discussion an abnormal T-wave occurred with a small R-wave in Leads V_2 and V_3 . Presumably, more definite changes in the initial ventricular deflections were absent because the infarct was located well back in the septum, was patchy in distribution, and was well surrounded by normal muscle fibers, especially in its anterior portion.

The third case (Figs. 8 and 9) is unusual in several respects. The important abnormalities of the special electrocardiograms are the small R-wave in leads from the midprecordium, and the short RS deflection in Leads V_4 and V_5 . The T-wave is abnormal on the left, but at least part of this abnormality can be attributed to digitalis.

It may be worth while to speculate on the cause of the small R-wave. Since in direct or semidirect leads this deflection depends on electrical forces generated by the passage of excitation through the adjacent ventricular wall,¹¹ it might, theoretically, be diminished in at least three ways: (1) by functional reduction of these forces, (2) by replacement of large numbers of muscle fibers by fibrous tissue, and (3)

by subendocardial infarction of such limited degree and extent as to diminish or delay the electrical forces normally contributed by the involved muscle. Ordinarily a direct lead in the region of such an infarct yields a "marginal" type of curve with a prominent initial negative deflection.¹ In the circumstances hypothesized, it might give an R-wave of small size. In the present case it seems that the sclerosis of the endocardium with involvement of a thin layer of adjacent myocardium, principally in the anterior wall of the left ventricle, and the multiple foci of scarring in the same region are sufficient to account for the observed diminution of the R-wave. One cannot be sure that these are the only factors, for the chest wall lies at some distance from the epicardial surface, and the effect of the variables which this spatial relationship introduces has not been ascertained. The miliary foci of necrosis seen at necropsy are of no significance so far as the curves presented are concerned, for the latter were recorded three months before death.

If the possible factors listed in the preceding paragraph are actually operative, it would appear that the abnormalities in the chest leads in Case 3 are not specific for myocardial infarction. In support of this contention we may refer to another case, not included here, in which the precordial potentials were very similar to those shown in Fig. 9. At necropsy the myocardium was the seat of advanced perivascular and interfascicular fibrosis caused by progressive coronary atherosclerosis and presumably by previous rheumatic infection. It is therefore possible for a small initial positive deflection to occur in leads from the middle or left side of the precordium when there is diffuse replacement fibrosis of the underlying ventricular wall. Obviously, the importance of being able to differentiate this clinically from a small subendocardial infarct is negligible.

The infarct in Case 2 was subendocardial, involving in most locations half or less of the thickness of the ventricular wall (Fig. 5). The chest leads showed a small R-wave in Lead V₂ and Lead V₃ (Fig. 7). The theory advanced above does not satisfactorily explain this small R-wave because it does not account for a typical "marginal" type of curve in Lead V₄. Moreover, it was shown at necropsy in Case 2 that the two leads mentioned were probably semidirect leads from the right ventricle. This, as indicated earlier, further complicates the matter. For the present, the facts must be accepted without complete explanation.

The Relative Value of Leads From One or Several Precordial Points.—It is well-known that infarction of the myocardium occasionally causes characteristic changes in the initial and final ventricular deflections of the precordial electrocardiogram when such changes are partially or completely absent from the standard leads.¹² It is not

so well-known that such changes are frequently definite at several precordial points and absent or indefinite at others. If a single apical lead had been taken with a small exploring electrode, the curve obtained in all of the four cases presented would have been similar to that from the anterior axillary line (Lead V_5), because the apex beat was well beyond the midclavicular line. In all four cases this lead is nearly the same (Figs. 4, 7, 9, 11). The abnormal T-wave indicates merely an abnormal recovery process which might be due to almost any cause whatsoever, including digitalis medication, while the QRS group, consisting principally of a large R-wave, gives no hint of the degree of pathologic changes which are clearly reflected in leads taken further to the right in three of the cases. The small Q-wave of this lead in Cases 1 and 3 is within normal limits.⁵ It would seem that the six leads used in the present work are not necessary in every case, but it is nevertheless clear that a single apical lead must often give incomplete or inconclusive information.

SUMMARY

The potential variations of the extremities and of six precordial points were correlated with the pathologic changes in four cases of infarction principally of the anterior wall of the left ventricle and, with one exception, of the anterior portion of the interventricular septum.

In the precordial electrocardiograms "central" and "marginal" patterns of the initial ventricular deflections similar to those obtained by Wilson, Johnston, and Hill in direct and semidirect leads in experimental infarction were easily recognized. The necropsy observations, however, indicate that several factors in addition to those held responsible for such curves in animals are probably of importance in human subjects.

In cases of infarction of the myocardium the additional and more conclusive information given by several leads, as compared with a single precordial lead, is made evident.

The authors are grateful to Dr. Frank N. Wilson for helpful criticism and suggestions.

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ACCURACY IN DIAGNOSIS AND LOCALIZATION OF MYOCARDIAL INFARCTION*

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THIS report is a correlation of the clinical, electrocardiographic, and pathologic observations in thirty-four cases of acute myocardial infarction studied at Lakeside Hospital. Special consideration has been given to the validity of the electrocardiographic evidence, both as to diagnosis and localization of the infarcts, and to errors in interpretation.

The subject of electrocardiographic changes in acute experimental and clinical myocardial infarction has been reviewed by Crawford and his coworkers,¹ Barnes,² Wolferth,³ and Wilson and his associates.^{4, 5, 6} Post-mortem examination of the heart in cases of myocardial infarction occasionally reveals no obstruction of major arteries. The area of infarction, therefore, is of prime importance, and the electrocardiographic diagnosis must relate to the area, rather than to occlusion of any particular coronary artery. The single infarctions are usually located in (1) the anterior, lateral, and apical part of the left ventricle (usually caused by obstruction of the anterior descending branch); (2) the posterior and basal portion of the ventricles (usually caused by obstruction of the left circumflex branch and occasionally by occlusion of the right coronary artery or the right descending branch); and (3) the interventricular septum (supplied by the septal branches of the right and left coronary arteries). Acute infarcts may be single or multiple, and may occur in hearts which are already the seat of old infarcts.

EXPERIMENTAL CORONARY ARTERY OCCLUSION

The electrocardiogram of acute experimental occlusion is characterized by a monophasic S-T and in many instances by the appearance of Q or an increase in the depth of an already existing Q. The infarct may be localized by studying the pattern of the changes in the Q-wave and S-T segments. Septal infarcts are often betrayed by prolongation of the P-R interval, dropped beats, A-V block, bundle branch block, or intraventricular block. The electrocardiographic changes caused by experimental occlusion of specific arteries are given in Table I.

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TABLE I
ELECTROCARDIOGRAPHIC PATTERNS FOLLOWING CORONARY ARTERY OCCLUSION*

ARTERY	PROLONGED A-V CONDUCTION PROLONGED INTRAVENTRICULAR CONDUCTION	Q ₁	Q ₃	S-T DEVIATION	CHEST LEAD (UPWARD DEFLECTION +)
<i>Experimental</i>					
Left descending branch	Infrequently	+	0	Ld. I + Ld. III -	QRS: initial wave deeply negative S-T deviation +
Left circumflex branch	Occasionally	0	+	Ld. I - Ld. III +	QRS: normal S-T deviation -
Right coronary artery	Occasionally	0	+	Ld. I - Ld. III +	QRS: normal S-T deviation -
Septal branch of left coronary artery	Left bundle branch block A-V block a late effect	0	0	Ld. I + Ld. III -	QRS: normal S-T deviation +
<i>Clinical</i>					
Left descending branch (Anterior, apical, lateral portion of the left ventricle)	Infrequently	+	0	Ld. I + Ld. III -	QRS: initial wave deeply negative S-T deviation +
Left circumflex branch (Posterior and basal portion of left ventricle)	Occasionally	0	+	Ld. I - Ld. III +	QRS: normal S-T deviation -
Septal branch of right circumflex artery (Septal infarct)	Occasionally	0	+	Ld. I - Ld. III +	QRS: normal S-T deviation -

Clinical Electrocardiographic Evidence of Infarction.—Herrick,⁷ in an important paper, described the clinical and electrocardiographic signs of acute coronary occlusion. It remained for Pardee⁸ to re-emphasize the importance of the electrocardiographic evidence and to study the localization of the infarcts on the basis of previous experimental work. In one of his cases there was pathologic confirmation of the electrocardiographic diagnosis, both as to the presence and location of the infarct. Pardee was the first to correlate the location of the infarct in the heart with the electrocardiographic pattern.

Parkinson and Bedford⁹ classified the electrocardiographic changes in their cases of recent coronary thrombosis as R-T₁ or R-T₃, depending on the characteristic elevation of R-T in the named lead of the standard electrocardiogram. They also divided the T-wave changes occurring two or three weeks following the infarction into T₁ and T₃ types, depending on whether T was negative in Lead 1 or Lead 3. In four of their cases autopsy confirmed their diagnoses. Wilson⁵ divided the changes into Q₁ and Q₃ types: Q₁ associated with anterior infarctions and Q₃ with posterior infarctions. Barnes,² in an extensive study of autopsy cases, found that it was possible to localize the infarcts with great accuracy. He concluded that the R-T₁ type was initiated by anterior and apical infarcts (caused by occlusion of the anterior descending branch), and that the R-T₃ type was caused by posterior and basal lesions, the result of occlusion of either the right coronary artery or the circumflex branch of the left coronary artery.

Wolferth and Wood¹⁰ increased the accuracy of electrocardiographic diagnosis, including localization, by the use of chest leads. In a recent report Wolferth¹¹ presented the electrocardiographic changes due to combinations of anterior and posterior infarcts, showing that the effect of the anterior infarct predominated and that the elevation of R-T₂ was greater than that of R-T₁.

Septal infarcts usually produce electrocardiograms showing various stages of A-V heart block or bundle branch block. Gross¹² stated that the upper septal branch comes from the right circumflex artery and anastomoses with the corresponding branch of the left coronary artery. He also stated that the right bundle branch is supplied invariably by one of the earliest branches of the anterior descending branch of the left coronary artery, and that the left bundle branch has no specific blood supply. White¹³ reported bundle branch block as one of the rapid changes in the electrocardiogram in a case of recent coronary thrombosis.

Table II correlates the electrocardiographic patterns in our cases with the location of the occlusions and infarcts.

Judging from experimental and clinical studies of recent myocardial infarction, a correct diagnosis and an accurate localization may be

TABLE II

CASE	ECG. DIAGNOSIS	AREAS OF ACUTE INFARCTION	AREAS OF OLD INFARCTION	ARTERIES THROMBOSED
1.	Ant. and apical	<i>B. proteus</i> abscess in anterior and apical portion of lt. ventricle		None
2.	Post. and basal (c)	Left ventricle. Ant. and post. at base. Upper $\frac{1}{3}$ of sep- tum	Left ventricle ant. and post. Focal in upper $\frac{1}{3}$ of septum	<i>Recent</i> in rt. and left cir- cumflex coronary. <i>Old</i> in right coronary
3.	Anterior (c)	Lower $\frac{1}{3}$ of left vent. ant. Lower $\frac{1}{3}$ of septum	In rt. and lt. vent. post.	<i>Recent</i> in ramus desc. of left. <i>Old</i> , right coronary artery
4.	Anterior	Lower $\frac{1}{3}$ of lt. and rt. vent. ant. Entire septum		<i>Recent</i> , left coronary
5.	Anterior (b)	Lower $\frac{2}{3}$ of lt. vent. ant. Lower $\frac{1}{3}$ of rt. vent. ant. Ant. lower $\frac{1}{2}$ of sep- tum	Ant. left vent.	<i>Recent</i> in ramus descen- dens of left coronary <i>Old</i> in ramus descendens of left coronary
6.	Posterior		(3 mo.) at post. wall of left vent. at apex	None
7.	Anterior (d)	Lower $\frac{1}{3}$ of lt. vent. anterior Focal in septum	Upper $\frac{1}{3}$ of lt. vent. Post. upper post. $\frac{1}{3}$ of septum	<i>Old</i> , right coronary <i>Old</i> , ramus descendens of left coronary
8.	Anterior	Lower $\frac{2}{3}$ of lt. vent. ant. Entire septum	Lower $\frac{1}{3}$ of lt. vent. ant. Lower $\frac{1}{3}$ of rt. vent. ant.	<i>Recent</i> , ramus desc. of left coronary <i>Old</i> , right coronary
9.	Anterior Septal (b) (a)	Lower $\frac{2}{3}$ lt. vent. ant. Lower $\frac{2}{3}$ lt. vent. post. All of septum	Focal of rt. vent. ant. and post.	<i>Recent</i> , ramus desc. of left coronary <i>Old</i> , right coronary
10.	Anterior Posterior (e)	At tip of lt. and rt. vent. ant. At tip of septum Below sulcus lt. vent. post.		<i>Recent</i> , small branches (microscopic)
11.	Anterior (c)	Lower $\frac{1}{3}$ of lt. vent. ant. Ant. lower $\frac{1}{2}$ and post. upper $\frac{1}{2}$ of septum Upper $\frac{1}{2}$ lt. vent. post. Right auricle lat. portion—micro.	Lower $\frac{1}{3}$ of lt. vent. ant.	<i>Remota</i> , ramus descendens of left coronary

(a) Left bundle branch block

(b) Intraventricular block

(c) Auricular fibrillation

(d) No chest lead

(e) Prolonged P-R interval

TABLE II—CONT'D

CASE	ECG. DIAGNOSIS	AREAS OF ACUTE INFARCTION	AREAS OF OLD INFARCTION	ARTERIES THROMBOSED
12.	Posterior Septal	At base of left vent. post. Upper portion of septum	Multiple of lt. vent. ant. Multiple of lt. vent. post.	<i>Recent</i> , right coronary <i>Old</i> , left circumflex and ramus descendens of left coronary
13.	Anterior	Lower $\frac{2}{3}$ of left vent. ant. Lower $\frac{2}{3}$ of septum	Upper $\frac{1}{3}$ lt. vent. post. Focal of lt. vent. ant. Post. of upper $\frac{1}{3}$ of sept.	<i>Recent</i> , ramus descendens of left coronary <i>Old</i> , right coronary
14.	Anterior	Lower $\frac{1}{3}$ of lt. vent. ant. Lower $\frac{1}{3}$ of rt. vent. Lower $\frac{1}{3}$ of septum	Focal and mult. of lt. vent. ant. Focal and mult. of lt. vent. post.	<i>Recent</i> , ramus descendens of left coronary <i>Old</i> , right coronary
15.	Posterior	Upper $\frac{1}{3}$ of lt. vent. post.		<i>Recent</i> , left coronary
16.	Anterior	Lower $\frac{2}{3}$ of lt. vent. ant. Lower $\frac{2}{3}$ septum Lower $\frac{2}{3}$ lt. vent. post.	Focal of lt. vent. post. Focal of sep- tum	<i>Recent</i> , ramus descendens of lt. coronary <i>Old</i> , right coronary
17.	Anterior	Lower $\frac{2}{3}$ lt. vent. ant.	Diffuse of lt. vent. ant.	<i>Recent</i> , ramus descendens of lt. coronary
18.	Anterior	At apex of lt. vent. ant. Tip and margin of septum		<i>Recent</i> , ramus descendens of left coronary
19.	Anterior	At apex of lt. vent. ant. with rupture Lower $\frac{1}{2}$ of septum		<i>Recent</i> , ramus descendens of lt. cor. <i>Recent</i> , lt. circumflex
20.	Anterior	At apex of lt. vent. ant. At apex of rt. vent. ant. Ant. apical portion of septum		<i>Recent</i> , ramus descendens of lt. coronary
21.	Posterior	Post. wall of lt. vent. post. repre- senting the lesion responsible for the recent infarction		<i>Recent</i> , right coronary <i>Old</i> , right coronary <i>Old</i> , left circumflex
22.	Posterior Septal	Multiple throughout both vent. and sep- tum		<i>Recent</i> , right coronary <i>Recent</i> , left coronary
23.	Posterior (c) (d)	Posterior wall of lt. vent. post. and postpapillary muscle	Fibrous of lt. and rt. vent. ant. and post.	<i>Recent</i> , almost complete atheromatous occlusion near origin of right coronary <i>Old</i> , marked coronary sclerosis

TABLE II—CONT'D

CASE	ECG. DIAGNOSIS	AREAS OF ACUTE INFARCTION	AREAS OF OLD INFARCTION	ARTERIES THROMBOSED
24.	Anterior	At apex of lt. vent. ant.	Posterior wall of lt. vent.	<i>Recent</i> , ramus descendens of left coronary <i>Old</i> , right coronary
25.	Anterior	Apical region of lt. vent. ant. Almost entire sep- tum		<i>Recent</i> , 8 cm. from origin of ramus descendens of lt. coronary
26.	Post and basal	Post. portion along margo obtusus of l.v. from base to apex	Throughout l.v. from base to apex show small scarred areas	Marked sclerosis, tip of l. cor. In places less than 1 mm. in diameter
27.	Anterior and apical	L.v. ant. with area 2 cm. in diam. of softening at apex. Mural thrombus on endocardium at this site	Throughout en- tire l.v. is the seat of old fibrosis	In descendens just after its division from lt. cor. a large calcified plaque was found and lumen at this point was less than 1 mm. Immediately distal to the plaque the artery was occluded for 1 cm. by a white atheroma
28.	Posterior and basal	In posterior wall of rt. vent. near post. portion of septum an area of 2.5 cm. Posterior one-half of septum from base to apex		None

attained in a high percentage of cases. The infarcts may be localized clinically as anterior, posterior, combined anterior and posterior, septal, and auricular, and the vessel which is occluded may often be named, but there are cases in which the thrombosis involves only the arteriolar supply of the area infarcted, leaving the large vessels patent. Arterial anomalies may likewise introduce errors. Abscesses and metastatic tumors of the heart may produce electrocardiographic changes resembling those of infarction.

METHOD OF TAKING ELECTROCARDIOGRAMS

The records include the conventional leads in all cases and, in most instances, chest leads. The latter were taken from the fifth left costal cartilage and from the apex, using the right arm wire for the exploring electrode and the left leg wire for the indifferent electrode. Following Wilson's method, we have recently changed the connections so that an upright deflection now indicates relative positivity of the precordial electrode. We have been using the left arm wire for the exploring electrode and the right arm wire for the indifferent electrode. In four instances a complete precordial survey was made by the technique of Wilson,¹⁴ employing the central terminal for the indifferent electrode (R.A., L.A., and L.L.).

Thirty-four cases of acute myocardial infarction, in which the diagnosis was substantiated at autopsy, were studied. There were twenty-nine males and five females. Four patients were colored. In three instances electrocardiograms had been taken previous to the occurrence of the infarct. The electrocardiographic diagnosis of recent infarction was correct in twenty-eight cases (82.05 per cent). (Table III.)

TABLE III
RÉSUMÉ OF THE PATHOLOGIC FINDINGS

AREAS OF INFARCTION	PATH. LOCALIZATION	ECG. LOCALIZATION	ERRORS*
Anterior	6	4	2 (Cases c and f)
Posterior	5	5	
Anterior and posterior	1		1 (Case b)
Anterior and septal	13	1 (10 diagnosed anterior)	2 (Cases c and d)
Posterior and septal	2	1 (1 diagnosed posterior)	
Anterior, posterior, and septal	4	1 (diagnosed ant. and post.) 2 (diagnosed post. and septal)	
Anterior, posterior, septal (basal and apical)	1	1 (diagnosed posterior and septal)	
Anterior and posterior at apex and septal and auricular	2	1 (diagnosed anterior, Case 11) 1 (diagnosed posterior and septal, Case 10)	

*These cases are discussed separately later in this paper.

Table IV shows which arteries were thrombosed. The frequency of multiple thromboses is evident. Infarction of the right auricle occurred in two cases (Cases 10 and 11). In Case 11, auricular fibrillation with frequent ventricular extrasystoles was present. There was also infarction of the anterior lower third and of the posterior upper third of the interventricular septum. In addition, there was old and recent infarction of the lower third of the left ventricle anteriorly, and recent infarction in the upper third of the left ventricle posteriorly. A partially occlusive thrombus was found in the anterior descending branch, midway between its origin and the apex, together with severe generalized coronary arteriosclerosis. In Case 10 the electrocardiogram (Fig. 1) shows regular sinus rhythm, sinus arrest, ventricular escape, and prolongation of the P-R interval. T_1 is tall and peaked; S- T_2 and S- T_3 are monophasic; and Q_3 is abnormally deep. Lead IV, taken from the fifth left costal cartilage, shows a deeply negative monophasic S-T. Lead V, from the apex, shows an elevated and monophasic S-T with a sharply negative T. The chests

TABLE IV
INCIDENCE OF THROMBOSIS IN THE CORONARY ARTERIES IN 34 CASES

OCCLUSION OF RIGHT CORONARY NEAR ORIGIN	OCCLUSION OF LEFT CORONARY NEAR ORIGIN		OCCLUSION OF ANTERIOR DESCENDING BRANCH		OCCLUSION OF LEFT CIRCUMFLEX BRANCH		SMALL ARTERIES SUPPLY- ING ANTERIOR PART OF APICES OF BOTH VENTRICLES AND ADJACENT SEPTUM, UPPER POSTERIOR SURFACE OF LEFT VENTRICLE		GENERALIZED SEVERE CORONARY SCLEROSIS
	OLD	RECENT	OLD	RECENT	OLD	RECENT	OLD	RECENT	
Case 13 Case 14 Case 16 Case 24 Case b	Case 2 Case 9 Case 12 Case 21 Case 22 Case b	Case 12 Case 22 Case d	Case 7 Case 11 Case 12 Case e	Case 3 Case 4 Case 5 Case 8 Case 9 Case 13 Case 14 Case 16 Case 17 Case 18 Case 19 Case 20 Case 24 Case 25 Case e Case e Case 27	None	Case 2 Case 15 Case 19 Case 21 Case f	None Case 10	Case 6 Case 7 Case 11 Case 23 Case a Case f Case 26	
Number of Thromboses in Each Coronary Artery									
5	6	1	2	4	17	1	5	1	7

leads (IV and V) were recorded with the right arm wire attached to the exploring electrode. Autopsy showed that there was a recent infarct of the lower third of the anterior portion of both ventricles and the tip of the septum. There was another infarct in the posterior and central portion of the heart involving the left ventricle and

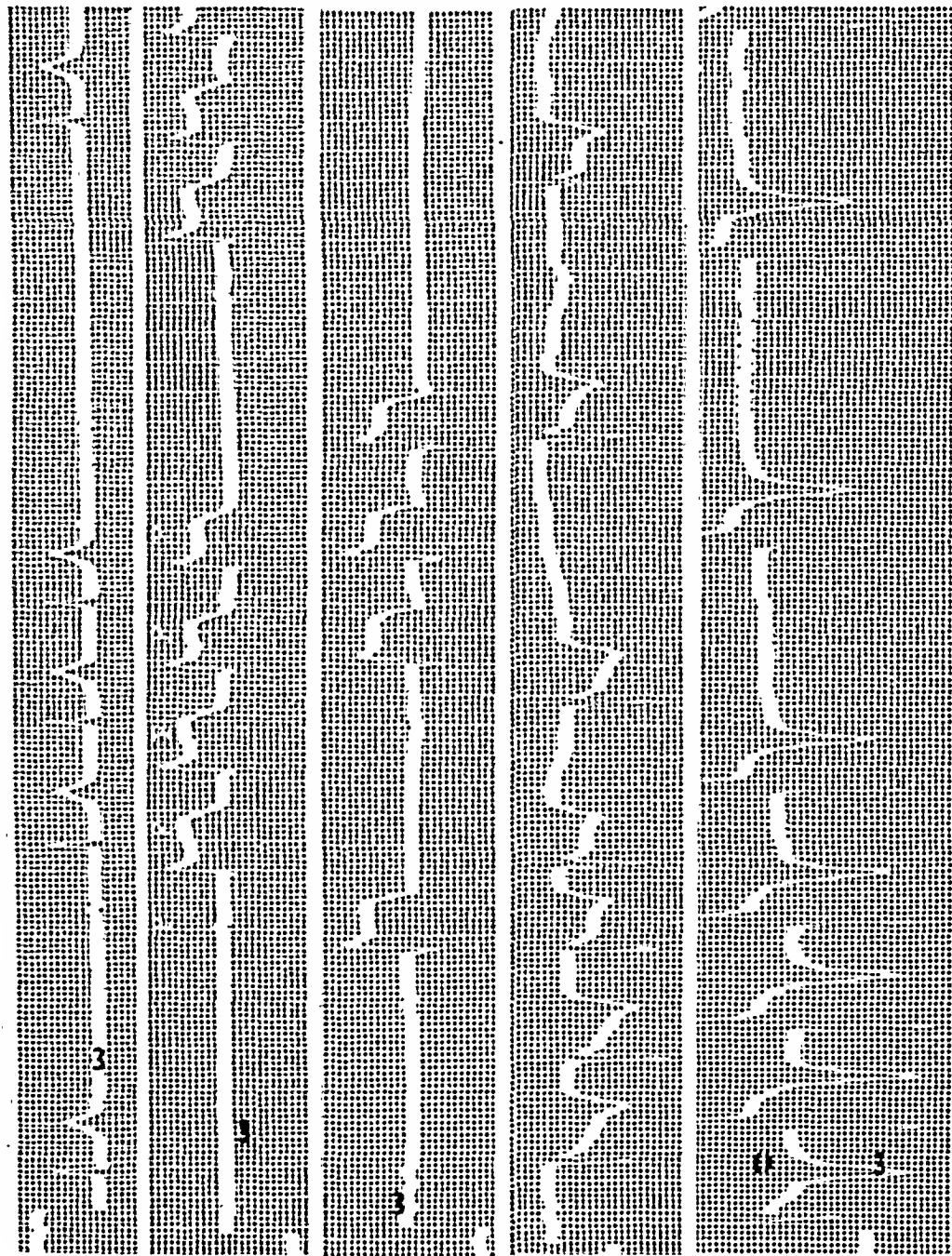


Fig. 1.—Case 10, see text.

septum. There was clotted blood, much of which was hyalinized, in the interstices of the muscle bands of the right auricle. The small coronary twigs in this area showed marked sclerosis and thickening.

Cardiac Rhythm.—Regular sinus rhythm was found in 27 cases; ventricular extrasystoles were present in 7 cases; and auricular fibrillation was present in 5 cases, 2 from the beginning of the infarction and 3 during the progress of the illness. A-V nodal rhythm occurred

in 2 cases; in one of these it was replaced by regular sinus rhythm, and in the other it changed to auricular fibrillation. Auricular flutter occurred in one case, to be superseded later by normal rhythm.

Axis Deviation.—Left axis deviation occurred in 18 cases, right axis deviation in one case, and no axis deviation in 15 cases.

Conduction Defects.—Complete A-V block occurred in one case; intraventricular block, in 4 cases; left bundle branch block, in 4 cases; and right bundle branch block, in one case.

Value of Chest Leads.—In 4 cases the diagnosis could be made by chest leads alone. In none of the cases were the chest leads normal. Of 28 cases in which the electrocardiographic diagnosis was confirmed post mortem, the conventional leads were diagnostic in 19. In 4 of these cases the chest leads (from the fifth left costal cartilage and from the apex) made the electrocardiographic evidence more convincing. Evidence of posterior infarction was obtained more frequently in the lead from the fifth left costal cartilage, and of anterior infarction in that from the apex.

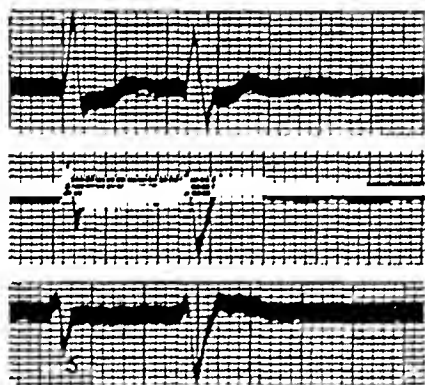


Fig. 2.—Case a, see text.

ERRORS IN ELECTROCARDIOGRAPHIC DIAGNOSIS

1. (Case a) M., aged 65 years, was admitted to the hospital because of congestive cardiac failure due to arteriosclerotic disease with moderate hypertension. The patient was digitalized and died of progressive failure on the fourth hospital day. The electrocardiogram (Fig. 2) showed auricular fibrillation, left axis deviation and frequent ventricular extrasystoles. There was nothing in the ventricular complex to suggest old or recent myocardial disease. Post-mortem examination: Heart weight, 445 gm.; old and recent infarction of the anterior and lower third of the interventricular septum and of the left ventricle near the apex. The anterior descending branch showed arteriosclerotic changes but no thrombosis. This error may have been due to the lack of chest leads.

2. (Case b) M., aged 61 years, was admitted to the hospital with congestive cardiac failure of eight months' duration. There was a history of retrosternal pain four days prior to admission to the hospital. The patient had been digitalized before admission. The clinical diagnosis was arteriosclerotic heart disease with hypertension, and diabetes mellitus. For four months the patient had slight precordial pain which radiated to his left arm. Four or five days previous to admission, he

became dyspneic and had precordial pain. There was slight peripheral edema. Blood pressure was 140/80. He received digitalis and salyrgan; on the third hospital day he was placed in an oxygen tent but died on the fourth hospital day. The electrocardiogram (Fig. 3A), taken one month before admission, showed left axis deviation, S-T₁ depressed 1.5 mm., S-T₂ depressed 0.5 mm., S-T₃ elevated 0.5 mm., and S-T₄ depressed 0.5 mm. (right arm wire exploring electrode and left leg wire indifferent electrode). An electrocardiogram taken on the second hospital day (Fig. 3B), showed normal sinus rhythm, left axis deviation, a P-R interval of 0.21 sec., S-T₁ depressed 1 mm., S-T₂ very slightly elevated, S-T₃ elevated 1 mm., notching of QRS in all leads, and a diphasic T-wave in the chest lead. The voltage was reduced. The definite changes in the second record, i.e., the elevation of S-T₂ and S-T₃ with depression of S-T₁, suggested posterior infarction, but this evidence was

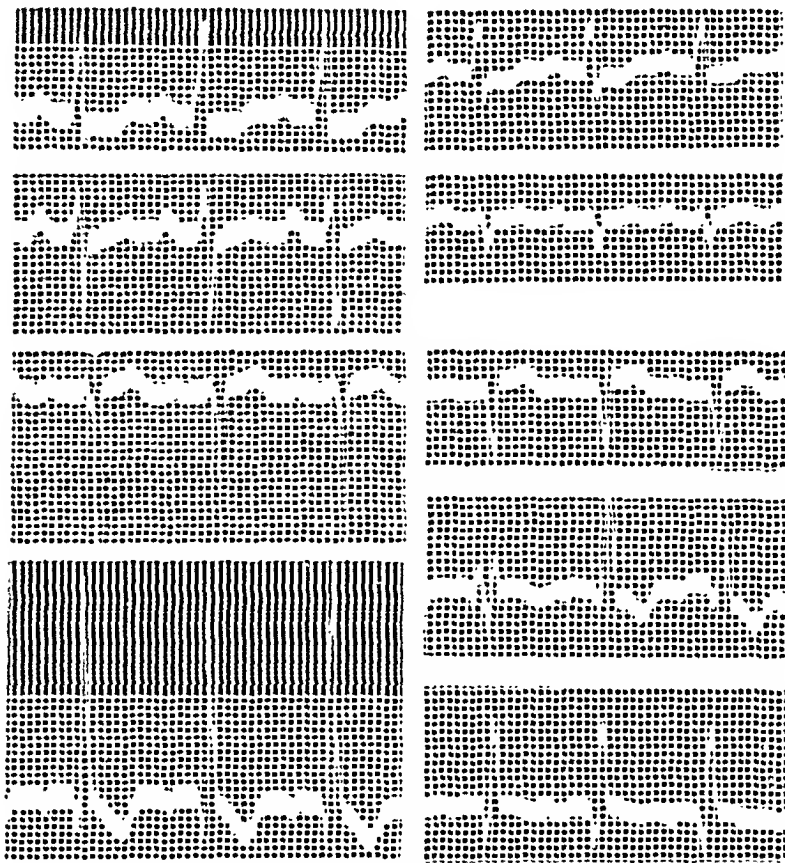


Fig. 3.—Case b, see text.

not sufficient for a positive diagnosis. At autopsy, the heart, which weighed 650 gm., showed mural thrombi in the right auricle and right ventricle, old fibrosis of the septum, a large infarction both old and recent in the posterior portion of the right ventricle near the base, and an old infarction with a recent spotty infarct of the right ventricle anteriorly. An old thrombus in the right coronary artery was overlaid by a recent occlusive thrombus. The right auricle was infarcted. Marked calcification and atheromatous changes were seen in the other coronary arteries. Although the electrocardiogram was not definitely diagnostic of recent infarction, the rapid change should have aroused strong suspicions.

3. (Case c) M., aged 59 years, was admitted to the hospital with an attack of severe dyspnea which had lasted three weeks. Substernal oppression occurred a few days before admission. The blood pressure was 180/140. On the fifth hospital day the patient died suddenly while expelling an enema. The electrocardiogram taken on the second day of hospitalization showed regular sinus rhythm and left bundle branch block (Fig. 4A). A second record taken on the fifth hospital day (Fig. 4B)

showed regular sinus rhythm. The bundle branch block had disappeared. Occasional ventricular extrasystoles were seen. The chest lead (anteroposterior) showed

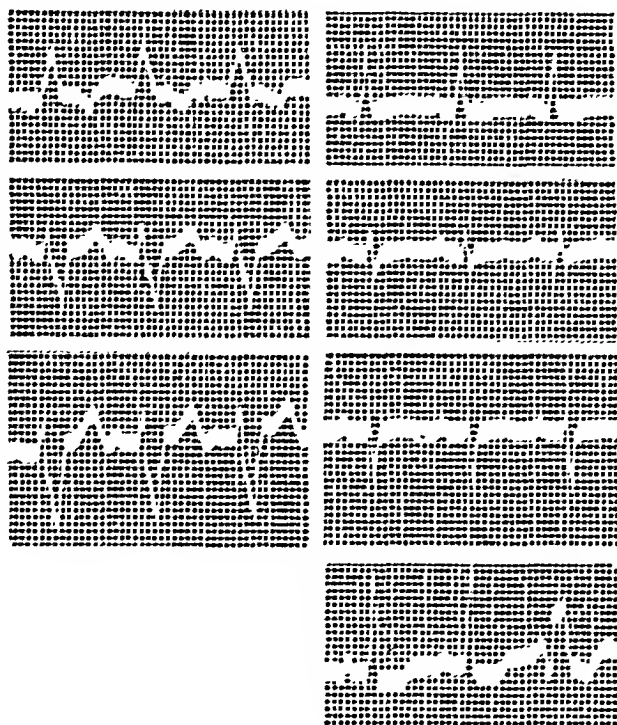


Fig. 4.—Case c, see text.

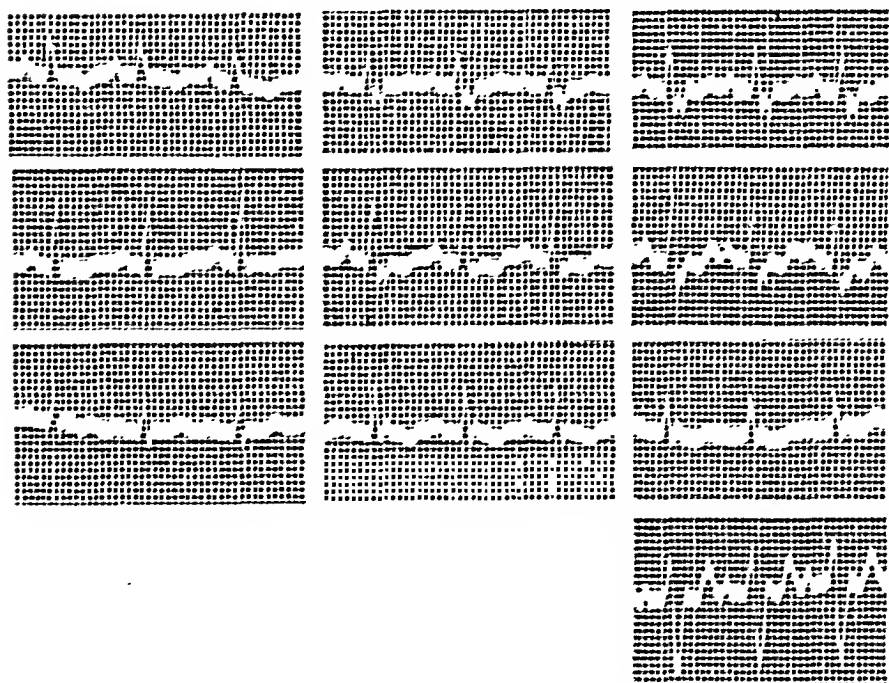


Fig. 5.—Case d, see text.

no Q-wave, and S-T was depressed 1.2 mm. The rapid changes in the electrocardiogram and the absence of Q₁ were diagnostic of recent infarction of the anterior surface of the heart. The temporary left bundle branch block was diagnostic of

septal infarction. Post-mortem examination revealed that the heart weighed 660 gm. Old and recent infarction of the septum (left side) and old and recent infarction of the anterior portion of the left ventricle were found. A recent thrombus was present in the anterior descending branch of the left coronary artery.

4. (Case d) M., aged 67 years, was admitted to the hospital because of severe retrosternal pain for eight hours. There was a history of postprandial retrosternal pain which had increased in frequency for a period of two years. On admission to

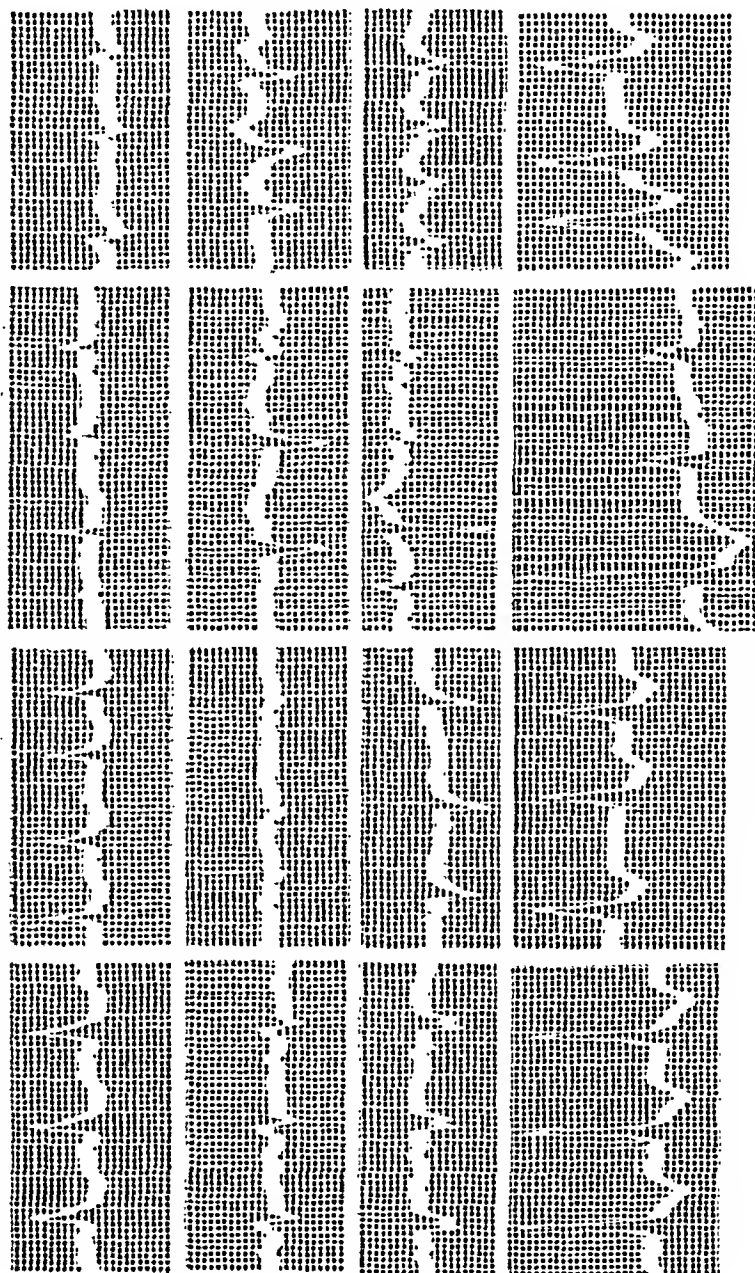


Fig. 6.—Case c, see text.

the hospital he had congestive cardiac failure. The blood pressure was 168/116. Death occurred on the seventh hospital day. The electrocardiogram taken on the first hospital day (Fig. 5A) showed regular sinus rhythm, widening of QRS₁, and a Pardee type S-T₁ and S-T₂ with inversion of T. No chest lead was taken. This record suggested a remote myocardial infarct, involving the anterior portion of the heart. A record taken on the third hospital day (Fig. 5B) showed regular sinus rhythm and defective conduction in the right bundle branch. The previously negative T₁ became positive. A record taken on the fifth hospital day (Fig. 5C) showed no changes in Leads I, II or III, but the chest lead (anteroposterior) showed no Q, and T was upright and tall. Clinically, this patient had coronary thrombosis, and

this diagnosis was confirmed by the rapidly changing electrocardiogram. This case might well have been included with those which were diagnosed correctly. Post-mortem examination showed that the heart weighed 500 gm. and that there were old and recent infarcts of the lower anterior third of the septum and of the lower half of the left ventricle anteriorly. A recent thrombosis was found in the anterior descending branch at its origin.

5. (Case e) F., aged 61 years, was admitted to the hospital for the first time because of cardiac decompensation. The clinical diagnosis was arteriosclerotic heart disease with hypertension (blood pressure, 170/115). The electrocardiogram showed regular sinus rhythm and left bundle branch block (Fig. 6A). The patient was digitalized and discharged as improved. Again, five months later, she was admitted because of cardiac decompensation and severe precordial pain. A friction rub was heard on the second hospital day. The patient had leucocytosis, a little fever, and

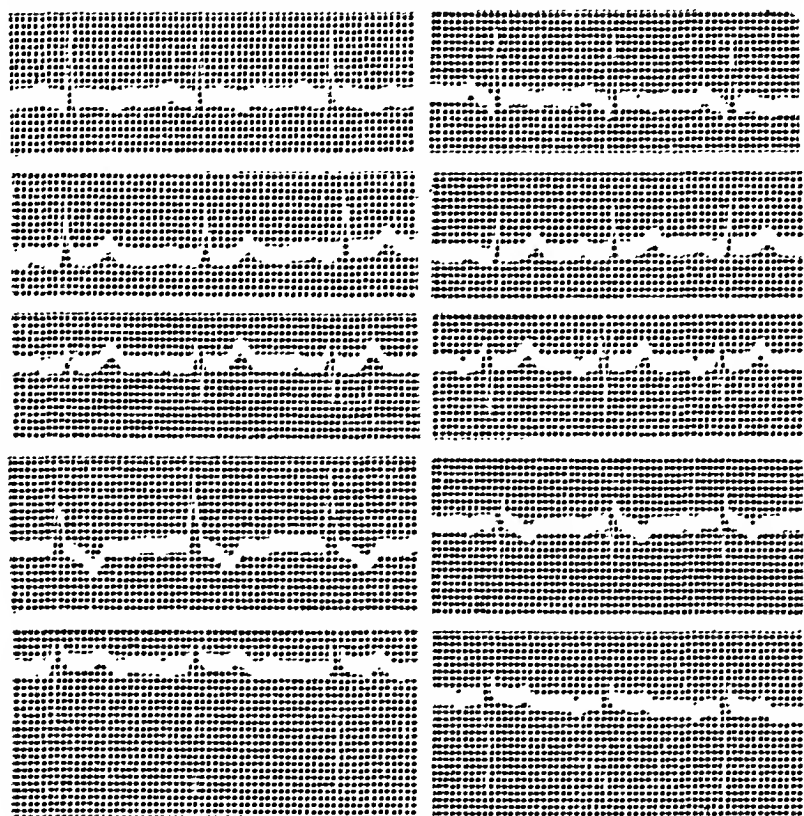


Fig. 7.—Case f, see text.

heart failure. A clinical diagnosis of old and recent myocardial infarction was made. The electrocardiogram showed wandering pacemaker and left bundle branch block (Fig. 6B). A record taken on the second hospital day showed, in addition, ventricular extrasystoles. Eleven days later there occurred a varying intraventricular conduction defect (Fig. 6C), and twenty-seven days later the record showed a striking change, again with evidence of intraventricular conduction disturbances (Fig. 6D). The congestive failure grew worse steadily, and the patient died one day after the last record was made. The post-mortem examination showed that the heart weighed 450 gm., and was the seat of diffuse myocardial fibrosis and a recent infarct at the tip of the left ventricle. An old and recent thrombus was found in the anterior descending branch 3 cm. from its origin.

6. (Case f) M., aged 60 years, was admitted to the hospital because of moderately severe substernal pain radiating to the left arm. The pain lasted three days.

Three years previously he had had an attack of indigestion which confined him to bed for two days. Subsequently the patient had been in good health. The clinical diagnosis at the time of this admission was arteriosclerotic heart disease with hypertension (blood pressure 190/110), coronary sclerosis, and recent coronary occlusion. The electrocardiogram on the first hospital day showed normal sinus rhythm and left axis deviation; Q_1 was present; S-T₁ was very slightly elevated; T₁ was inverted; and T₂ was upright. (The right arm wire was connected to the exploring electrode and the left leg wire to the indifferent electrode.) (Fig. 7A.) A diagnosis of myocardial disease was made. A record two days later (Fig. 7B) was much the same. The abnormalities were consistent with myocardial changes due to fibrosis, the result of remote coronary occlusion. The clinical diagnosis of recent coronary occlusion was not confirmed by the electrocardiogram. One day later the patient died suddenly. Post-mortem examination showed that the heart weighed 500 gm.; it was the seat of fibrosis in the greater part of the septum, and there was evidence of a remote infarct in the left anterior half of the septum; old and recent infarcts were found in the anterior surface of the left ventricle, and rupture of the myocardium through the central part of the infarct (over the anterior papillary muscle) had occurred. There was calcification of the left circumflex artery with recent thrombosis of the other coronary arteries.

DISCUSSION OF ERRORS

The records of patients with hypertensive arteriosclerotic heart disease, especially when digitalis has been administered, may be somewhat confusing. Atypical curves suggesting posterior and basal infarcts may be due to acute right ventricular strain caused by recent multiple pulmonary infarcts. In the curves of the latter condition there is a deep S₁, and the depression of S-T₁ and elevation of S-T₂ are not striking. In the chest lead the typical S-T deviation is not present (Barnes¹⁵). Pericarditis with and without effusion causes elevation of S-T, but this is usually present in all leads and there is no complementary depression. Likewise the chest lead is helpful, as it is not always monophasic. The history in all of the above conditions may assist in the diagnosis.

In six patients (Table V) having myocardial infarction at post-mortem examination, the electrocardiographic changes were not sufficiently definite to confirm the clinical diagnosis of coronary occlusion.

In summary, one error may have been due to lack of chest leads. In one case with successive records the diagnosis could not be made. In four cases there was suggestive evidence which, if taken with the history in three cases, should have led to the diagnosis of recent coronary thrombosis. In the one case in which successive records were made and no electrocardiographic evidence of recent coronary thrombosis was found, necropsy disclosed fibrosis of the septum, old and recent myocardial infarction near the base and old infarction of the right ventricle anteriorly, with recent spotty infarction in the same area. This anterior and posterior infarction of the right ventricle, both old and recent, may have been responsible for the absence of confirmatory electrocardiographic evidence. In none of the six cases was the electrocardiogram entirely normal.

TABLE V

CASE	ECG. DIAGNOSIS	AREAS OF ACUTE INFARCTION	AREAS OF OLD INFARCTION	ARTERIES THROMBOSED
a.	Auricular fib. with many vent. extrasystoles	Mural thromb. on septum Areas of myomalacia near apex region	Areas of old myomalacia near apex region	Sclerosis of ramus descendens of left coronary artery
b.	Changes in record suggested myocardial involvement but not conclusive for infarction	Right vent. post. and lateral—spotty infarction right vent. ant. Rt. auricle. Mural thrombi in right auricle and ventricle	Right vent. post. and lateral fibrosis of septum and right vent. ant.	<i>Recent</i> , right coronary; marked sclerosis of other coronaries
c.	Shifting pacer-maker evidence of myocardial damage	Tip of lt. vent. ant.	Diffuse fibrosis through ant. heart	<i>Recent</i> , ramus descendens of lt. cor. <i>Old</i> , ramus descendens of lt. coronary
d. 1.	Changed to normal	Lower $\frac{2}{3}$ of lt. vent. ant. and lt. side of septum	Lower $\frac{2}{3}$ of lt. ventricle ant. and lt. side of septum	<i>Recent</i> , ramus descendens of lt. coronary
2.	Sinus rhythm with depression S-T ₁ (old method). Absence of Q ₁			
e. 1.	Pardee S-T ₁ and 2 Inverted T ₁	Lower $\frac{1}{2}$ of lt. vent. ant. and ant. lower $\frac{1}{4}$ of septum	Lower $\frac{1}{2}$ of lt. vent. ant. and ant. lower $\frac{1}{4}$ of septum	<i>Recent</i> , ramus descendens of lt. coronary
2.	With upright T ₁			
3.	With upright T ₁ and absence of Q ₁			
f. 1.	Inverted T ₁ and upright T ₄	Apex of lt. vent. ant. with rupture through central portions	At apex of lt. vent. Fibrosis of greater portion of septum	<i>Recent</i> , lt. circumflex <i>Old</i> , lt. circumflex
2.	Same as No. 1 and S-T ₁ is Pardee type			

Infarction of the right ventricle (Table VI) alone occurred in only one case in this series. This patient had hypertensive arteriosclerotic heart disease with congestive failure. Angina played no part in the clinical picture. The electrocardiogram showed suggestive but not conclusive evidence of a posterior and basal infarct. The right coronary artery was obstructed 5 cm. from its origin by a recent organized thrombus which was superimposed on an older thrombus. In six cases acute infarction of the right ventricle occurred in combination with infarction of the left ventricle. In four of these, the left ventricle anteriorly and the septum were involved. In one case both the anterior and posterior portions of the left ventricle and the septum were infarcted. In this case the electrocardiographic diagnosis was posterior and septal infarction. In the remaining case the anterior portion of

TABLE VI
INFARCTION IN RIGHT VENTRICLE

CASE	RECENT INFARCTION		OLD INFARCTION	INFARCTION ELSEWHERE	ECG.
	ANTERIOR	POSTERIOR			
3.			At base of left and right vent. post.	Recent in ant. left vent. and septum	Anterior
4.	Multiple, lower $\frac{1}{3}$			Recent lower ant. $\frac{1}{3}$ of lt. vent. and entire septum	Anterior
5.	Multiple, lower $\frac{1}{3}$			Recent lower $\frac{2}{3}$ of lt. vent. and lower $\frac{1}{3}$ of septum	Anterior
9.			At base of rt. vent. ant. and post.	Recent lower $\frac{2}{3}$ of left vent. ant. and all of septum	Anterior and septal
10.	Multiple, tip of right vent.			Recent tip of lt. vent. ant. and post. Recent below sulcus of lt. vent. post.	Anterior and posterior
8.			Old lower $\frac{1}{3}$ of rt. vent. ant.	Recent lower $\frac{2}{3}$ lt. vent. ant. and entire septum	Anterior
14.	Multiple, lower $\frac{1}{3}$ rt. vent.			Recent lower $\frac{1}{3}$ lt. vent. ant. and lower $\frac{1}{3}$ of septum	Anterior
20.	Multiple, apex			Recent at apex of lt. vent. ant. and apical portion of septum	Anterior
22.	Multiple	Multiple		Recent multiple of lt. vent. ant and post. and septum	Posterior and septal
23.			At base of rt. vent. ant. and post.	Recent of post. wall lt. vent. and post. papillary muscle.	Posterior
28.		Single, at base		Recent post. $\frac{1}{2}$ of septum, base to apex	Posterior and basal
29.	Multiple, lower $\frac{1}{3}$. Mural thrombi	Multiple, at base			In cases of error

the apex and the posterior surface of the left ventricle near the auriculoventricular sulcus were the seat of infarction. In the latter case the electrocardiogram fulfilled the criteria of Wolferth¹¹ (Fig. 1).

SUMMARY

Of 34 cases of recent myocardial infarction in which necropsy was performed, the clinical and electrocardiographic diagnosis was correct in 28 (82.05 per cent). In the 6 undiagnosed cases there was some electrocardiographic evidence in 3, and none in the other 3 cases. These diagnostic errors were due to lack of chest leads in one case, left bundle branch block in 2 cases, and intraventricular block in one case; in 2 cases the evidence was suggestive, but not conclusive. In 21 cases pericarditis was present at autopsy, but in none were the electrocardiographic changes typical of those seen in acute pericarditis.

Multiple acute infarction without previous infarction was present in 8 cases (24 per cent), and in 22 cases the recent infarction, both single and multiple, was associated with older infarction.^{16*} In the case of acute single infarction alone the accuracy of diagnosis and localization was 100 per cent. In the cases of recent and old infarction accuracy of diagnosis and localization was 73 per cent. In the diagnosed cases the accuracy of the electrocardiographic localization of the major acute infarction was 100 per cent (28 cases).

The diagnosis of acute myocardial infarction should be made from the patient's history, the physical examination, and laboratory findings.¹⁷ The electrocardiogram (especially when serial records and chest leads are taken) will assist in the diagnosis and localization of infarction in over 80 per cent of the cases.

We wish to thank Dr. A. R. Moritz, Pathologist of Lakeside Hospital, for his assistance in the analysis of the post-mortem data.

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*Right auricular infarction occurred in two cases.

Department of Clinical Reports

COARCTATION OF THE AORTA AT AN UNUSUAL SITE, ASSOCIATED WITH A CONGENITALLY BICUSPID AORTIC VALVE

REPORT OF CASE*

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COARCTATION of the aorta is one of the congenital anomalies which lends itself to precise recognition during life. The case which we are reporting not only emphasizes the salient features of coarctation of the aorta, but is of interest because the site of the narrowing bore an unusual relationship to the origin of the left subclavian artery. The exact anatomic diagnosis was made clinically despite the fact that evidence of collateral circulation could not be elicited. The clue, in fact, to the correct diagnosis was afforded by the unusual anatomic arrangement. The absence of corroborative signs was regarded as attributable in part, at least, to the extreme degree of circulatory failure present when the patient was first seen.

Coarctation of the aorta has been classified into the so-called adult and infantile types. The infantile form consists of a diffuse narrowing of the aorta between the origin of the left subclavian artery and the point of insertion of the ductus arteriosus. The ductus arteriosus remains patent, and the situation may be regarded as an exaggeration of the anatomic arrangement that exists normally in the fetus. The adult type of coarctation is rarely associated with a patent ductus arteriosus. The narrowing of the aortic isthmus is abrupt, and the degree of stenosis amounts in some cases to complete obliteration of the aortic lumen at the site involved, with the result that an extensive collateral circulation develops.

The pathologic changes and the theories of pathogenesis of this lesion have been adequately considered in the reviews of Bonnett,³ Abbott,¹ Hamilton and Abbott,⁵ and Blackford,² and it is unnecessary to discuss them here.

REPORT OF CASE

A man, twenty-six years of age, was admitted directly to the cardiac service at the Worrall Hospital in an obviously critical state of congestive failure. The details of his history were meager as well as difficult to obtain. He apparently had

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always experienced excellent health and had led a very active life, enjoying more than average physical strength and endurance, as was necessary in his occupation, which was that of a farm laborer. Three months before his admission to the hospital he first had noted moderate dyspnea on exertion and weakness of the legs. Both of these symptoms had become progressively more severe until two weeks prior to his admission to the hospital, when he had begun to have paroxysmal attacks of dyspnea, and edema of the legs had developed. Despite these symptoms of circulatory failure he had remained ambulatory until three days before his admission to the hospital. Approximately 60 minims (4 c.c.) of tincture of digitalis had been administered daily without benefit.

Physical examination revealed a well-developed and well-nourished young man. He was continuously orthopneic but had only slight cyanosis. The respiratory rate was between 40 and 50 per minute and the pulse rate was 120 per minute; there were visibly exaggerated pulsations of the carotid arteries. The temperature was 98.4° F. There was moderate edema of the legs, and the liver extended about 2½ inches below the costal margin. Coarse râles were present at the bases of both lungs. The heart was enlarged and the apical impulse was visible in the fifth intercostal space to the left of the anterior axillary line. The tones were of poor quality, and a definite gallop rhythm was present. A rough systolic murmur and a blowing diastolic murmur could be heard over the aortic area.

The finding of a marked disparity in the volume of the two radial pulses immediately aroused our attention. The pulse in the right radial artery was large and of a forceful "water-hammer" quality, whereas that in the left radial artery was so small as to be hardly palpable. The blood pressure in the right arm was 210/40 mm. Hg, and in the left arm, 100/78 mm. Hg. No pulsation could be felt in the abdominal aorta or in the arteries of the legs. Whereas the pulsations in both carotids and the right subclavian were very prominent, careful palpation over the left subclavian artery revealed almost no pulsation at all. Careful search did not disclose any evidence of increased collateral circulation.

Routine examination of the urine did not reveal any abnormality except moderate albuminuria (Grade 2). The concentration of hemoglobin was 11.9 gm. per 100 c.c. of blood; the erythrocytes numbered 3,540,000, and the leucocytes 24,100, per cubic millimeter of blood, respectively. The flocculation test for syphilis was negative. The value for the blood urea was 90 mg. per 100 c.c. Roentgenologic examination of the thorax did not reveal any evidence of erosion of the ribs. The heart was enlarged, there was congestion of the lungs, and the aorta appeared to be dilated. The electrocardiogram showed left ventricular preponderance, incomplete bundle branch block (QRS, 0.14 sec.), inverted P-waves in Lead III, and delayed A-V conduction (P-R, 0.28 sec.), and the Wolfersht Lead IV showed inverted T-waves, diminished Q-waves, and notched QRS complexes.

The diagnosis was coarctation of the aorta at or above the level of the left subclavian artery, chronic rheumatic endocarditis, aortic insufficiency, and cardiac decompensation. The patient failed to respond to supportive treatment, and anuria developed. This was assumed to be secondary to circulatory insufficiency. The patient died on the fourth day after his admission to the hospital. In view of the post-mortem findings, it is interesting to note that he remained afebrile while under our observation. Necropsy disclosed marked enlargement of the heart, tremendous hypertrophy of the left ventricle, and dilatation of the right and left ventricles. The heart weighed 855 gm. An abrupt coarctation of the aortic isthmus was found, reducing the lumen at this point to only 8 mm. The aorta showed marked dilatation distal to the site of coarctation, but the proximal segment was smaller than normal. The ductus arteriosus consisted of a thick, firm, fibrous cord measuring 3 to 5 mm. in diameter; its lumen was completely obliterated, and its point of insertion

into the aortic wall was immediately proximal to the site of coarctation. The abnormally small left subclavian artery arose just distal to the coarctation, and the normal left carotid artery sprang from the arch of the aorta immediately proximal to the site of stenosis (Figs. 1, 2 and 3).



Fig. 1.—Coarctation of aorta showing relationship of aorta and vessels: *a*, site of coarctation; *b*, left subclavian artery; *c*, left common carotid artery; *d*, thickened and obliterated ductus arteriosus. The aorta distal to the coarctation is dilated and is relatively small proximal to it.



Fig. 2.—Coarctation of aorta (aorta and other vessels opened); *a*, thin constricting band arising above the subclavian artery; *b*, subclavian artery; *c*, left common carotid artery; *d*, site of attachment of the obliterated ductus arteriosus.

Examination of the heart disclosed a congenitally bicuspid aortic valve; both leaflets were involved in an extensive vegetative endocarditis. Fragile subacute vegetations covered the greater portion of both aortic leaflets and there had been

extension of the process along the adjacent endocardium of the left ventricle (Figs. 4 and 5). The mitral, tricuspid and pulmonary valves appeared normal. The heart measurements were as follows: Aortic valve 8 cm., mitral valve 12.5 cm., tricuspid valve 16 cm., pulmonary valve 10 cm. The depth of the left ventricle was 10 cm., and the thickness of its wall was 1.8 cm. The depth of the right ventricle was 12 cm., and its wall was 0.4 cm. thick. Both internal mammary arteries were appreciably enlarged, and there was a general increase in size of the intercostal vessels; there was also enlargement of the thymic artery. Complete necropsy did not reveal anything else significant except evidence of chronic passive congestion. The liver was enlarged and weighed 2280 gm., and the spleen weighed 455 gm. A small infarct was present in the right kidney and another was found in the base of the right lung. Examination of the brain did not reveal any evidence of embolism, or of congenital aneurysm of the vessels constituting the circle of Willis.

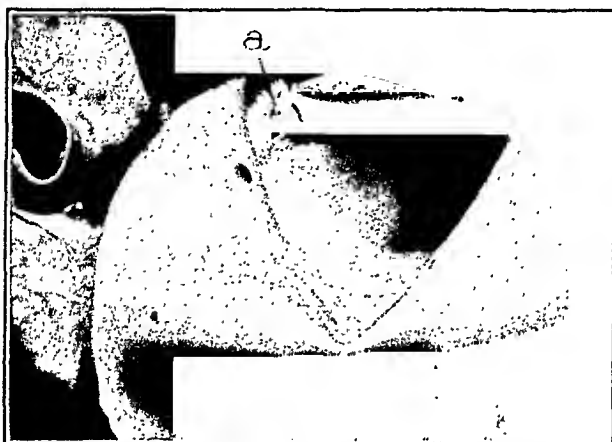


Fig. 3.—Coarctation of aorta; view of the aorta from below the coarctation, showing the marked degree of aortic constriction; the lumen at *a* measured 9 mm. in diameter.

COMMENT

The presence of high brachial arterial pressure without corroborative evidence of true essential hypertension is often the initial clue which leads to the diagnosis of coarctation of the aorta. The classic findings of elevated blood pressure in the upper extremities in contrast to a reduced pressure in the lower extremities, small or absent pulsations in the abdominal aorta and arteries of the legs, and associated evidence of collateral circulation in the upper part of the body are important criteria of coarctation. A significant disparity in the pulse volume and blood pressure in the two arms, however, has not been of frequent occurrence in proved cases of coarctation.

King⁶ has made an exhaustive review of the blood pressure measurements in the reported cases of this anomaly. Of 175 cases, there were 66 in which the blood pressure in both arms was recorded. In only 10 of these was there an appreciable difference in the blood pressure in the two arms. Unfortunately, necropsy information was available only in the case reported by Woltman and Shelden.⁷ The blood pressure in this case was 164/86 in the right arm, and 126/110 in the left arm.



Fig. 4.—Marked ventricular hypertrophy and dilatation contrasted with heart of normal size below; the fact that the aortic valve is bicuspid and is the seat of vegetative endocarditis is well demonstrated.



Fig. 5.—Close-up of the bicuspid aortic valve and vegetative endocarditis.

Necropsy disclosed that the proximal portion of the left subelavian artery consisted only of a fine ligamentous cord; the distal part of the artery was the recipient of extensive collateral vessels. In a recent case reported by Borgard⁴ the elinical appearance was typically that of coaretation. In addition, there was associated evidence of obstruction to the left subelavian artery, from which he concluded that the site of coaretation was proximal thereto.

In Abbott's review¹ of 200 cases recorded in the literature, there were six in which anatomic study showed that the stenosis was definitely "above the ductus," and in seven others it was described as situated at or above the origin of the left subelavian artery. These figures would indicate that the anatomic relations which existed in our case are relatively rare.

One of the interesting features of our case was the presence of a congenitally bicuspid aortic valve. It is indeed not uncommon to find defects in the vascular system associated with coaretation. Bonnett³ and Abbott¹ have called attention to the fact that the grave and complex forms of associated anomalies, such as biloculate or triloculate heart, transposition of the aortic trunks, and pulmonary atresia, are commonly combined with the infantile type of coaretation. The minor congenital variations, such as bicuspid aortic valve, anomalous origin of the arteries from the arch of the aorta, and defects of the aortic septum and subaortic stenosis, occur frequently in the adult type of coaretation. A congenitally bicuspid aortic valve was found in 25.1 per cent of Abbott's series of cases.

Another feature of interest in our case was the presence of subacute vegetative endocarditis of the bicuspid aortic valve. Although the presence of coexisting valvular disease and aortic insufficiency was diagnosed before death, we did not suspect the true nature of the lesion. The patient had remained afebrile, and except for the presence of leucocytosis, there was no indication of an inflammatory process. Furthermore, there was no elinical evidence of embolic phenomena. This again, however, must call our attention to the fact that the possible development of bacterial or vegetative endocarditis is one of the most constant hazards in congenital heart disease. One may well wonder whether the myocardium might have remained compensated if this lesion had not been present. Undoubtedly the degree of coaretation present in this case imposes a no small burden on the heart; yet in the presence of a normal myocardium without the superimposed inflammatory process, the heart in all probability would have carried this burden for many years without noticeable circulatory deficiency. Abbott's statistics show that the highest mortality occurs between the

second and third decades of life; however, cases in which the patients live beyond the fifth and sixth decades of life are not uncommon.

In cases of coarctation death usually results from progressive myocardial failure. Other common causes are rupture of the heart, rupture of the aorta, the development of an aneurysm, either aortic or cerebral, and endocarditis.

SUMMARY

We have reported a case of coarctation of the aorta in which the site of stenosis was between the left common carotid and the left subclavian arteries. The condition was diagnosed during life and proved by post-mortem examination. The case reported is of further interest because of the presence of a congenitally bicuspid aortic valve which was the seat of subacute vegetative endocarditis.

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THROMBOANGIITIS OBLITERANS IN A WOMAN*

REPORT OF A CASE

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IT IS well known that thromboangiitis obliterans rarely affects women, but no adequate explanation has ever been given. Only about twenty-two satisfactory cases are on record. In Buerger's series¹ of 500 cases there were 2 women; in Koyano's series² of 120 there was one; in Horton and Brown's series³ of 700 there were 10; in Herrell and Allen's series⁴ of 350 there was one; and in Silbert's series⁵ of 1,200 there were 2. In addition, single cases have been reported by Meleney and Miller,⁶ Telford and Stopford,⁷ Dürk,⁸ Traubaud and Chaty,⁹ Traubaud and Mredde,¹⁰ and Van Dellen and Wright.¹¹

REPORT OF CASE

S. K., a married Russian Jewish woman, 27 years of age, was admitted to the hospital May 11, 1937, and discharged July 8, 1937. She gave a history of intermittent claudication due to pain in the calf of the right leg of two years' duration. Two weeks before admission severe pain developed in the fifth right toe, which became infected and discolored. During her fourth pregnancy, three years before, she had had some "trouble" with the veins in both legs. The patient had been a cigarette smoker for many years, and in the two years preceding admission had smoked between 40 and 60 cigarettes a day. Once every year, for ten years, she had taken about 2 ounces of the fluidextract of ergot to induce abortion. The last dose was taken four months before admission. She had always noticed numbness and tingling of the extremities soon after taking the drug.

Physical Examination.—There were no abnormalities except in the lower extremities. Both feet were cold, the right more so than the left. Dependent rubor and blanching with elevation were very evident in both legs. No pulse could be felt in either dorsalis pedis or posterior tibial artery. There was a small area of gangrene on the fifth toe of the right foot.

Oscillometric Readings

	<i>Foot</i>	<i>Ankle</i>	<i>Below Knee</i>	<i>Mid-Thigh</i>
Right	0	0	0	1½
Left	0	1	1	1½

The blood pressure was 90/60. Ophthalmoscopic examination showed nothing remarkable.

Laboratory Examination.—The electrocardiogram was normal. Roentgenograms of the feet and legs revealed no evidence of calcification of arteries. The basal

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metabolic rate was -3 per cent. Agglutination tests for the presence of typhoid, paratyphoid, and typhus antibodies were negative. The Kline test was negative. The blood calcium was 9.7 mg. per cent; the nonprotein nitrogen of the blood, 29.8 mg. per cent; the blood cholesterol, 170 mg. per cent; and the plasma protein, 6.73 gm. per cent (albumin 3.85 gm. per cent, globulin 2.9 gm. per cent, albumin-globulin ratio 1.3). The hemoglobin was 85 per cent; the erythrocytes numbered 4,400,000; and there was a slight leucocytosis. Blood volume studies gave the following result:

Hematocrit (packed cells)	43.3 per cent
Plasma volume	2108 c.c.
Total blood volume	3703 c.c.
Blood volume per kilogram	68 c.c. (85 c.c. is normal)

Subsequent Course.—During the first month of her stay in the hospital the patient received 250 c.c. of a 5 per cent salt solution intravenously every forty-eight hours. Thereafter, for one month, she received 3 c.c. of tissue extract (Sharpe and Dohme) intramuscularly every forty-eight hours. When she left the hospital the gangrenous area was healing, but there was still no pulse in the dorsalis pedis artery. Treatment with 5 per cent salt solution was continued in the outpatient department.

Examination Oct. 26, 1937, showed that the gangrenous area had healed, but there was no pulse in the dorsalis pedis or posterior tibial artery, and the right foot was still colder than the left.

Oscillometric Readings

	<i>Foot</i>	<i>Ankle</i>	<i>Below Knee</i>	<i>Mid-Thigh</i>
Right	0	0	0	2
Left	0	1½	1½	3

Except for moderate claudication due to pain in the right calf, she felt perfectly well.

COMMENT

Silbert and his associates,^{12, 13, 14} in their study of thromboangiitis obliterans, found that the basal metabolic rate was low, that the blood was concentrated and its volume reduced, and that the amounts of blood proteins, calcium, and cholesterol were increased. In my case none of these abnormalities except reduced blood volume was noted.

It is doubtful if ergot played an etiologic role in this case. The patient had taken only 10 doses in ten years, and there had never been a severe local reaction.

CONCLUSION

The foregoing case is reported because of the rarity of thromboangiitis obliterans in women. The patient was a young Russian Jewess who had abused tobacco, gave a history of intermittent claudication, and had a painful, gangrenous area on one toe. Dependent rubor and pallor with elevation were evident in both legs, both feet were cold, and no pulse could be felt in either dorsalis pedis or posterior tibial artery. There was no evidence of peripheral arteriosclerosis.

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ACUTE ISOLATED MYOCARDITIS

REPORT OF A CASE, WITH A STUDY OF THE DEVELOPMENT OF THE LESION* †

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THE term "acute isolated myocarditis," now used instead of "acute primary myocarditis," should designate a disease in which inflammation of the myocardium is the only important active acute lesion in the body. The disease may be due to actual infection of the myocardium, or, as in experimental animals and very probably in man, to the effect of chemical action alone or chemical and other factors acting simultaneously on the heart. In some cases the etiology remains obscure, hence the term "idiopathic." The disease regularly runs its full course without being recognized, despite the fact that it has been periodically considered and quite well defined in the foreign medical literature during the past thirty-six years. It is only recently that a few reports have appeared in the American literature. Our recent experience with a case prompted us to make a survey of the literature, from which we learned that there is a group of symptoms which seem distinctive. Our survey was extended to include the various chemicals used singly or in combination in the experimental production of acute myocarditis. We wished to know particularly whether experimental myocarditis paralleled acute isolated myocarditis in severity of injury and reaction. Our own case afforded an unusually good opportunity to study the development of the myocardial lesions. By reporting it, and summarizing the important clinical and pathologic characteristics of all the cases in the literature, we hope to facilitate the diagnosis of this elusive disease.

REPORT OF CASE

Clinical Examination.—C. G. (105252), a well-developed and well-preserved colored woman, 48 years of age, entered the Gallinger Hospital, Washington, D. C., Oct. 17, 1933, and died suddenly Oct. 20, 1933. She had suffered since early in the summer of 1933 from what she called a bad chest cold, which was followed by cough and the expectoration of a large amount of frothy sputum. The sputum was twice bloodstained. The patient complained of much weakness and said that she had lost 20 pounds. She thought that she had had fever at times, but her temperature had not been taken. She continued to do her housework until two weeks before her admission to the hospital, when she was forced to go to bed because of extreme weakness, shortness of breath, and fever. The only gastrointestinal findings of note were blood in the feces on two occasions and a filling defect at the pylorus which was thought to be caused by spasm. She had been treated for syphilis, but did not remember when, for how long, or by what means.

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The temperature on admission was 99.6° F., and the blood pressure was 100/79. The gums were puffy and bled easily, the teeth were carious, and there was enlargement of the cervical lymph nodes. A few râles were heard at the apices of both lungs. The heart was normal to physical examination. A definite mass which was thought to pulsate was felt in the midline in the epigastric region; the epigastrium was tender and tense. The liver was palpable.

Clinical Laboratory Examination.—The hemoglobin was 80 per cent. The leucocytes numbered 18,000 per cu. mm., and the differential leucocyte count showed that 50 per cent were lymphocytes, 2 per cent large mononuclear cells, 44 per cent polymorphonuclear cells, and 3 per cent nonfilamented polymorphonuclear cells. The Kahn test was strongly positive.

Clinical Course.—The temperature varied from 99° to 99.6° F. until the day before death, when it rose to 102° F. The pulse rate ranged from 100 to 110, and the respiratory rate from 20 to 28. There were no complaints other than weakness and

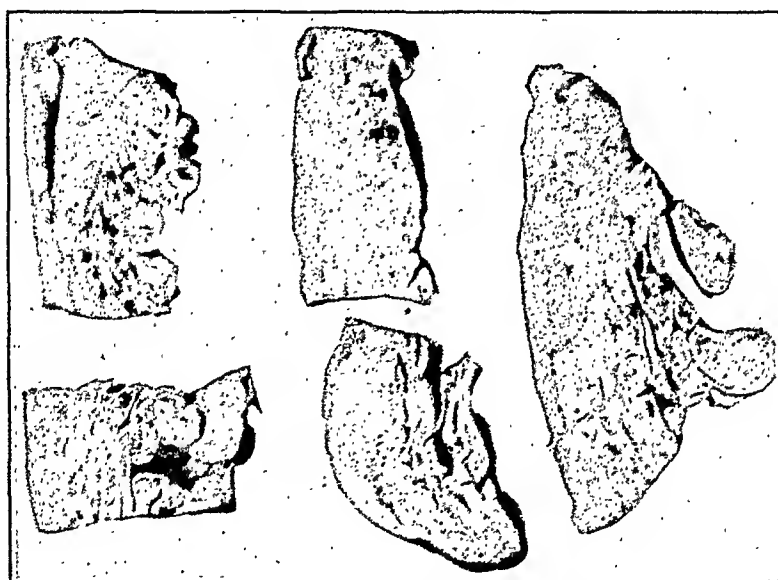


Fig. 1.—Cut sections of the myocardium. The gray appearance and the numerous hemorrhagic foci are striking.

dyspnea. On the evening of October 21, the patient felt very uncomfortable and restless, and $\frac{1}{4}$ grain of morphine sulfate was administered. One hour later she was found dead in bed.

Post-Mortem Examination.—The body was that of a well-developed and excellently nourished woman. *Rigor mortis* was marked. Cyanosis of the finger tips, lips, and dependent portions of the body was extreme. There was no edema. The teeth were carious and the gums swollen. The layer of fat in the midline over the chest and abdomen was from 1 to 2 cm. thick. The internal genitals were the seat of an old, quiescent inflammatory process. Moderate enlargement of lymph nodes was found over the pericardium, in the region of the thymus gland, and in the neck and abdomen. The nodes at the hilum of the liver were especially enlarged, the largest measuring 2 cm. in diameter. The heart weighed 300 gm. and was normal as far as muscle mass was concerned. There was no dilation. The myocardium was somewhat gray and translucent. There were petechiae beneath the endocardium, including that of the papillary muscles, and the left ventricular surface of the interventricular septum contained large ecchymoses. On section, there were distinct gray areas about 2 mm. in diameter framed by a zone of hyperemia and hemorrhage. These lesions were most conspicuous in the left ventricle and interventricular septum, but were also

present, in descending order of frequency, in the right ventricle, right auricle, and left auricle. The lesions appeared to be contained entirely within the myocardium. The coronary vessels were normal. The pericardium and endocardium were smooth and glossy. The right lung weighed 250 gm., the left 220 gm.; the alveoli contained frothy fluid. The spleen weighed 110 gm.; it was not grossly abnormal. The duodenal mucosa was greatly congested, and the pancreas showed post-mortem digestion. The liver weighed 1,100 gm., and its edges were rounded. The hepatic veins were dilated. The right kidney weighed 125 gm., the left 150 gm.; both appeared normal. There were a few atheromatous plaques in the aorta. The bladder was not inflamed. The thyroid gland was normal in size, and its cut surface appeared normal. The trachea, larynx, and pharynx were removed, and appeared to be normal.

Histologic Examination.—The only important pathologic changes, other than the enlarged lymph nodes, were found in the myocardium, which contained lesions in various stages of development. The most recent lesions consisted of fractured hyalinized muscle fibers which had lost their striations, and in these areas definite hemorrhages were observed. Others which appeared to be further developed revealed, in addition to the muscle injury and hemorrhage, numerous polymorphonuclear leucocytes. Still others contained remnants of hydropic and fatty muscle fibers and many lymphocytes and large mononuclear cells. Many of the latter contained hemosiderin. There were also areas of quite well-developed scar tissue which was arranged in a columnar pattern as if it had replaced individual muscle fibers. A few myocardial giant cells were present in some of these areas. Here and there exudate extended into the interstitial tissue. The coronary vessels appeared normal. The remaining organs showed acute edema and congestion. The enlarged lymph nodes were simply hyperplastic. There was no histologic evidence of syphilis as described by Warthin. There was but slight atheromatous change in the aorta. The thyroid and adrenal glands were normal.

Bacteriologic Examination.—Smears and cultures made from the nose and throat at the time of post-mortem examination showed streptococci, but no organisms or colonies which resembled the *Corynebacterium diphtheriae*. Numerous sections of the myocardium stained by the Warthin-Starry method failed to reveal the *Treponema pallidum*, although organisms in control material were well stained. Bacterial stains also failed to reveal other organisms in the myocardium.

EPICRISIS

We have no reason to suppose that this patient suffered from anything other than myocardial injury after the beginning of her illness early in the summer of 1933. There was no evidence of generalized systemic infection, and therefore, if bacteria are to be held responsible for the myocardial injury, one must fall back on the somewhat doubtful assumption of focal infection. The patient had had leucorrhea, but the cervix did not appear to be particularly abnormal. The swollen gums and carious teeth were possible foci of infection. The outstanding clinical features were weakness, cyanosis, and dyspnea. The patient was well-nourished and appeared to be in good health throughout most of her illness, and there was no hypertrophy or dilation of the heart and no edema of the extremities. A priori, one would expect the lesions of isolated myocarditis to be evenly distributed. In this case they were most numerous in the wall of the left ventricle and the interventricular septum, which fact suggests that the higher left ventricular pressure

Fig. 2.

Fig. 3.

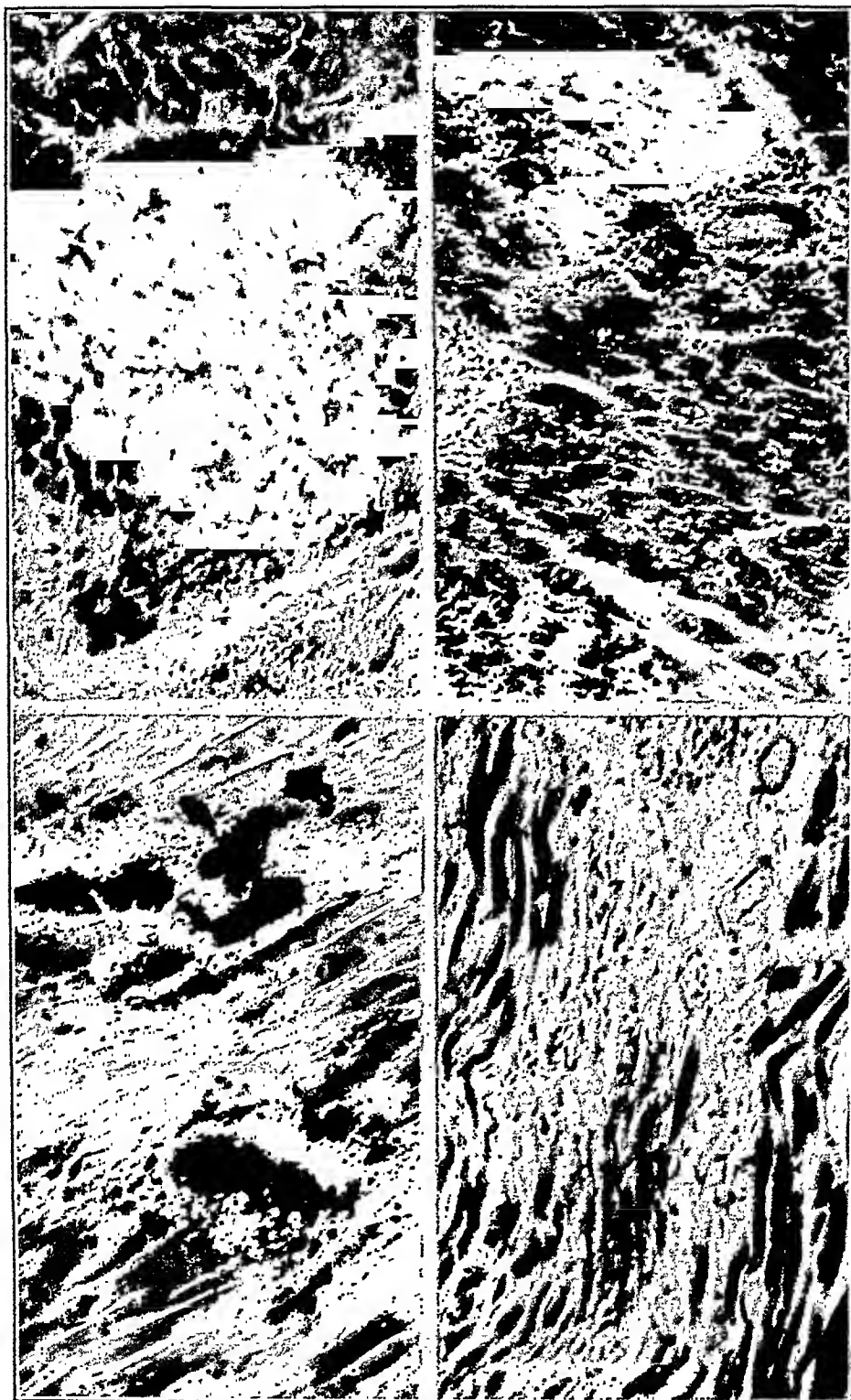


Fig. 4.

Fig. 5.

Fig. 2.—Photomicrograph ($\times 205$) showing an area of early injury to the myocardial fibers, as indicated by the intense staining reaction and early cellular infiltration.

Fig. 3.—Photomicrograph ($\times 205$) showing the diffuse inflammatory cellular infiltration within and between the muscle fibers.

Fig. 4.—Photomicrograph ($\times 250$) illustrating the fractured muscle fibers and hemorrhage. Many severely injured unfractured muscle fibers are also seen.

Fig. 5.—Photomicrograph showing the parallel arrangement of scar tissue in which fragments of muscle fibers are enmeshed.

may have been a factor in their distribution. The sequence of events in the development of the lesion appeared to be (1) injury of muscle fibers, (2) fracture of muscle fibers with hemorrhage, (3) leucocytic infiltration, (4) clearing away of fragments of tissue by macrophages, and (5) scarring. This is not unlike Zenker's degeneration of voluntary muscle. The fact that so many of the hyalinized muscle fibers were fractured makes one suspect that the same thing occurs in the milder forms of toxic myocarditis from which patients usually recover. It may be that the loss of these fibers increases the demands on those which survive, with the result that hypertrophy and dilation of the heart eventually occur. Moreover, this may explain the tremendous hypertrophy and dilation in cases in which the coronary arteries are not significantly narrowed and hypertension has not been a factor. Saltykow¹⁰ has also maintained that acute myocarditis leads ultimately to myocardial fibrosis and hypertrophy.

Acute isolated myocarditis was first described by Fiedler,⁵ who included in his report only cases in which the myocarditis was the sole lesion. Subsequent contributions have been made by Saltykow,¹⁰ Scott and Saphir,¹² de la Chapelle and Graef,³ Bailey and Andersen,¹ and others. Warthin¹³ described isolated myocarditis due to the *Treponema pallidum* which he interpreted as an acute exacerbation of chronic syphilitic myocarditis similar to the critical reaction observed by Brown and Pearce² in their experimental animals.

Not all authors have excluded, as Fiedler⁵ did, cases in which myocarditis was not the sole lesion. Many were complicated by systemic infection or by other kinds of heart disease. Those in which infection was present might not differ greatly from cases of myocarditis following diphtheria, scarlet fever, severe burns, or influenza. At best, it would be difficult to distinguish the symptoms referable to acute myocarditis from those which were caused by the accompanying condition.

The important clinical and pathologic features of *uncomplicated* acute isolated myocarditis, as recorded in the literature, are summarized in Tables I and II. The occupations are not tabulated, but sixteen different ones were represented. The close clinical similarity between this disease and coronary occlusion is striking. However, ten of the patients were rather young for coronary occlusion, and the extremely severe precordial pain which appears suddenly and tends to radiate is not characteristic of acute isolated myocarditis. Rapidly developing myocarditis is more likely to be signalized by comparatively mild precordial distress and a chill. The patient is restless, apprehensive, short of breath, cyanotic, and may complain of weakness, palpitation, and irregularity of the heart. By the time these symptoms have appeared the heart is usually enlarged, indicating that the pathologic process begins long before the symptoms. Therefore, if we are to discover the etiologic agent, we must

not neglect to question the patient carefully about the events, however trivial, of the months immediately preceding the first unequivocal symptom.

TABLE I

THE IMPORTANT CLINICAL FEATURES OF ACUTE ISOLATED MYOCARDITIS

CASE NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
AGE	53	42	45	25	45	44	57	22	53	35	22	42	24	21	21	39	26	48
DURATION (DAYS)	1	2	1	3	3	1	1	14	90	14	8	7	6	18	8	14	90	150
SYPHILIS	+	+	0				+								0			0
WASSERMANN									0	0				0			0	+
RESTLESSNESS	+								+		+	+	+	+		+	+	+
DYSPNEA	+		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
CYANOSIS	+	+	+	+		+			+	+	+	+	+	+	+	+	+	+
PRECORDIAL PAIN	+	+			+	+	+		+	+	+	+	+	+	+	+	+	+
WEAKNESS	+	+				+	+			+	+	+	+	+	+	+	+	+
FROTHY SPUTUM				+								+			+			+
ABDOMINAL PAIN	+												+			+		
ARM PAIN	+					+	+									+		
ENLARGED HEART									+	+		+	+		+		+	
FEVER									+	0	0	+	+	+	0		+	+
ARRHYTHMIA									+	+	+	+	+		+		+	
MODE OF ONSET	S	S	S	S	S	S	S				SC	G	SC	G	G	G	G	G
MODE OF DEATH	S	S	S	S	S	S	S		S	S			S	S	G	S	G	S
PALPITATION					+				+	+	+						+	
EDEMA										0	0	0	0	+		0	0	
LEUCOCYTOSIS														+	+			+
HEART RATE												152	148	38	140	92	140	110
SWEATING												+	+		0	+		0

LEGEND - + = PRESENT 0 = ABSENT S = SUDDEN G = GRADUAL
C = CHILL BLANK SPACE = NO STATEMENT

TABLE II

THE IMPORTANT PATHOLOGIC FEATURES OF ACUTE ISOLATED MYOCARDITIS

CASE NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
LYMPHOCYTES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEUTROPHILES	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+
PLASMA CELLS	+	+	+	+	+	+		+	+						0	+	+	+
MONOCYTES							+	+	+					+	+	+		+
EOSINOPHILES							+	+	+	+	+	+				+	+	+
GIANT CELLS							+							0		+	+	+
DILATION	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0
HYPERTROPHY	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0
MYOCARDIAL INJURY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+
PERICARDITIS			+					0	0	0					0	0	0	0
MURAL THROMBUS			+	+				+	+	+		0		+	+	+	0	0
CORONARY OCCLUSION								0	0	0	0	0	0		0			0
MYOCARDIAL HEMORRHAGE								+		+	+	+	+	+			+	+
MYOCARDIAL SCARRING	+	+	+	+			+				0	0	0	+		+	+	+
GENERAL EDEMA									+	+	0	0	0	+			0	0
SPIROCHETES	+	+	+	+	+	+	+								0		0	0
OTHER ORGANISMS										+	0	0	0	0	0	0	0	0

LEGEND - + = PRESENT 0 = ABSENT BLANK SPACE = NO STATEMENT

Except for the cases reported by Warthin, in which the *Treponema pallidum* was regularly demonstrated, investigators have been uniformly

unsuccessful in their search for bacteria in the myocardial lesions. Rindfleisch⁹ isolated an organism from the myocardium which he called *Staphylococcus citreus*, but it did not cause abscesses, and he was unable to demonstrate its presence histologically; its etiologic relationship to the lesions in the myocardium must be regarded as doubtful. Most authors are of the opinion that the myocardial injury is due to bacterial toxins circulating in the blood. The pathologic changes which have been described do not enable one to distinguish between the cases in which the *Treponema* was present in the tissue and those in which no organisms were found. The hypertrophy and dilation of the heart, the scarring in some of the lesions, and the myocardial giant cells indicative of a reparative process are the earmarks of a steadily progressive and insidious disease which leads to sudden and unexpected death.

The histologic examination in our case was very enlightening. The fact that lesions were observed in all stages of development betrayed the progressive nature of the disease. The myocardial injury was diffuse, but the development of focal defects seemed to be dependent upon fracture of the hyalinized muscle fibers, followed by hemorrhage, exudation, and the formation of scar tissue in columns which exactly replaced the original muscle fibers. The free ends of the affected muscle fibers were thus bound together. These observations indicate that the process is not primarily an interstitial one, as many previous authors have supposed.

Many chemical agents have been employed, alone or in combination, to produce acute experimental myocarditis. The best results have been obtained by combining sparteine with adrenalin, or chloroform with thyroxin or desiccated thyroid substance, but the lesions produced are not comparable in severity with those of acute isolated myocarditis. The fact that in acute infectious diseases the heart usually escapes and that acute isolated myocarditis is rare would indicate that more than one factor is concerned in acute myocarditis, and that one of these factors must be of bacterial origin (e.g., the diphtheria or streptococcus toxin).

In the final analysis, acute isolated myocarditis differs etiologically from the acute toxic myocarditis which is caused by infectious diseases only in that the origin of the infectious agent is obscure. We have already learned to recognize the cardiac complications of the infectious diseases and should experience still less difficulty with the diagnosis of acute isolated myocarditis, for the latter is not accompanied by the misleading protean manifestations of the generalized infectious process.

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Department of Reviews and Abstracts

Selected Abstracts

Freeman, Norman E., and Zeller, J. Wallace: The Effect of Temperature on the Volume Flow of Blood Through the Sympathectomized Paw of the Dog With Observations on the Oxygen Content and Capacity, Carbon-Dioxide Content, and PH of the Arterial and Venous Blood. *Am. J. Physiol.* 120: 475, 1937.

Experiments have previously been performed in humans, studying the effect of temperature on the rate of blood flow in the sympathectomized hand. The results of these studies suggested a dual control of the circulation, indicating that the flow of blood is modified by the vasomotor nerves to meet the requirements for thermoregulation of the body as a whole. After removal of the vasomotor control, the circulation seems to be dependent upon the metabolic requirements of the tissues. The results of the experiments as carried out in man were somewhat variable; this was considered to be due to reflex secretion of adrenaline induced by unavoidable emotional disturbances. In order to eliminate the adrenal factor, similar experiments have been carried out on dogs in which one adrenal gland had been removed and the other had been denervated. The oxygen content, carbon-dioxide content, and pH of the arterial and venous blood were studied in three unanesthetized, trained dogs in which one adrenal had been removed and the other denervated. The volume flow of blood in the sympathectomized paw of these animals was measured by plethysmographic determinations. It was found that the oxygen and carbon-dioxide contents and pH difference in the arterial and venous blood were constant in a single experiment over wide ranges of blood flow and metabolism. The volume flow of blood through the paw varied directly with the temperature of the bath in which the paw was immersed. These findings are consistent with the hypothesis that the circulation through regions deprived of vasomotor control is controlled by the metabolic needs of the tissues.

HINES.

László, T.: Physiology of Adrenal Cortical Hormones. *Cardiologia* 1: 219, 1937.

Simultaneous removal of both adrenals has no effect on the specific conducting system of the heart in dogs killed shortly before the time of expected death. Cortical extracts used in these studies, according to the author, were considered unsatisfactory, and the results may have been due to impurities rather than to the hormone itself.

KATZ.

Puddu, V.: Concerning the Action of Cardiac Nerves. *Arch. f. d. ges. Physiol.* 238: 467, 1937.

Observations on the dog show that the sympathetics change the electrocardiographic contour. Unipolar leads from the ventricles indicate that the right and left nerves have action on different regions. Following complete heart block in

the dog, it was found that vagus stimulation slowed the idioventricular rhythm. This is attributed to transmission of cholinergic material liberated in the auricle.

KATZ.

Rühl, A., and Thaddea, S.: Dynamics and Metabolism of Heart Poisoned With Monoiodoacetic Acid. *Ztschr. f. Kreislaufforsch.* 30: 26, 1938.

Monoiodoacetic acid in doses of 250-500 mg. caused pulmonary edema in the heart-lung preparation of the dog, and later damage to the heart. The coronary vessels showed a marked dilatation. The pulmonary edema can be delayed by prophylactic doses of strophanthin. Lactic acid consumption of the heart is increased by monoiodoacetic acid, and the glycogen content of the heart muscle is increased. The respiratory quotient is usually decreased. Muscular hemorrhages occurred and these probably explain the electrocardiographic changes.

KATZ.

Schneider, Edward C., and Collins, Raymond: Venous Pressure Responses to Exercise. *Am. J. Physiol.* 121: 574, 1938.

A comparison of the Eyster, Hooker, and White methods of determining venous pressure shows that each gives the same account of the changes that result from physical exertion.

The venous pressure rises and then remains up during work on the bicycle ergometer. In some individuals the pressure begins to rise almost at once, reaches a maximum within two to four minutes, and then maintains a fairly steady state. In others after some delay a slow rise begins, reaches a maximum within ten to twelve minutes, and then remains fairly constant until work is terminated.

When the load of work is too heavy, the venous pressure rises steadily until fatigue ensues.

There is a rough linear relationship between venous pressure and load. This may be obscured by the deep breathing of exertion, since during expiration the venous pressure may be as much as 2 cm. H₂O higher than during inspiration.

After physical exertion the venous pressure ordinarily slowly returns to normal. This may be accomplished within a few minutes, but after heavy work often requires as much as twenty-two to twenty-seven minutes.

AUTHOR.

Gibson, John G., and Evelyn, Kenneth A.: Clinical Studies of the Blood Volume. *J. Clin. Investigation* 17: 153, 1938.

A photoelectric method of determining the dye concentration of serum samples in the plasma volume method of Gibson and Evans is described.

Comparison of this method with that employing the spectrophotometer proves it to be accurate within a range of ± 2.5 per cent in a series of plasma volume determinations.

For purposes of clinical research the simplified technique is as reliable as the spectrophotometric method and possesses the added advantages of greater simplicity, economy, speed, and freedom from subjective errors.

AUTHOR.

Pezzi, C., and Agostoni, G.: Concerning Stenosis of the Aorta in the Region Between the Arch and Descending Portion. *Cardiologia* 1: 125, 1937.

In the authors' review of this subject, the greater frequency of that form of stenosis occurring where the ductus Botalli is situated, and the rarity of clinically

visible arterial collaterals in the thoracic region are pointed out. The x-ray picture is typical of stenosis of the aorta. It shows the enlarged left ventricle, the usually dilated ascending aorta, and the characteristic notching of the posterior lower margins of the ribs.

KATZ.

Rothberger, C. J.: Concerning the Normal and Pathological Physiology of the Specific Conducting Tissue of the Heart. *Cardiologia* 1: 234, 1937.

An excellent review is presented of the subject with which the author has long been identified. The article must be read for the details. Among the facts brought forth, the following may be mentioned: (1) the refractory phase of Purkinje fibers is longer than that of ordinary ventricular muscle; (2) as the strength of stimulus to the Purkinje fibers was decreased, failure to respond to some of the impulses was found to occur before the stage was reached where all became ineffective; (3) the duration of the electrogram of the Purkinje fibers is longer than its refractory phase and contraction, (4) veratrin in small doses leads to runs of beats with pauses between them and (5) Purkinje fibers are not as susceptible to low oxygen content as auricular strips.

KATZ.

Takino, M., and Watanabe, S.: The Significance of the Ligamentum Arteriosum of the Ductus Botalli and Its Junction with the Pulmonary Artery as a Blood Pressure Regulator in Various Animals. *Arch. f. Kreislaufforsch.* 2: 18, 1937.

In the embryo and young animal (rabbit, dog, cat, and fetus of man) this region contains end organs which set up reflexes to help adjust the circulation. As the ductus degenerates into a ligament, the end organs move from the aortic attachment to the pulmonary artery and still function.

KATZ.

Schellong, F., Schwingel, E., and Germann, H.: Vector Diagraphy and the Normal Vectordiagram. *Arch. f. Kreislaufforsch.* 2: 1, 1937.

This is a description of the method previously reported by the authors of using thoracic leads with stereoscopic orientation. In 100 normal persons the spatial contour of the vector diagram was determined during the inscription of the QRS complex and also during that of the T-wave. The QRS vector has an elliptical form which may be interrupted by flat indentations. It starts from zero and moves forward to the left and down and then backward to the right and then up. At its start it first moves up and at its end moves down. The T-wave forms a smaller similar ellipsoid. The angle between the end of the QRS and T ellipsoids is determined and was found in all but 4 cases to be less than 45 degrees. This spatial vector derived from thoracic leads is more satisfactory than the one derived from leads from the extremities.

KATZ.

Spang, R., and Korth, C.: Alternans of the Ventricular Complex of the Human Electrocardiogram. *Arch. f. Kreislaufforsch.* 2: 47, 1937.

The literature is reviewed by the authors and ten cases are reported. Alternans of groups of beats as contrasted with alternans between beats is described. One cannot separate electrical from mechanical alternans.

KATZ.

Hadorn, W.: Observations of the Heart in Hypoglycemic Shock (in Relation to the Electrocardiographic Changes in Insulin Treatment of Schizophrenia With Notes on the Effect of Cardiazol on the Electrocardiogram in the Same Condition). *Arch. f. Kreislaufforsch.* 2: 70, 1937.

This is a presentation of monographic proportions which covers over 80 pages and contains the author's extensive studies correlating work on animals and patients.

Insulin shock in schizophrenic and in normal subjects causes, in many persons, tachycardia and a rise in blood pressure with increased pulse pressure and venous pressure. Angina pectoris may also occur in diabetics with coronary sclerosis, but similar pain may be found in schizophrenics without heart disease. These changes are attributed in part to a liberation of adrenalin. It is concluded that insulin is to be used cautiously in coronary sclerosis.

In the electrocardiogram insulin causes increased amplitude of P and QRS, prolongation of QRS and P-R, coronary nodal rhythm, extrasystoles of auricular and ventricular origin, depression of S-T, prolongation of electrical systole, and flattening and inversion of T. These electrocardiographic changes indicate again the hazard of insulin usage in coronary disease. Cardiazol (tetrazol) causes much less change in the electrocardiogram than does insulin. There is, however, a tendency toward auricular extrasystoles and auricular fibrillation.

KATZ.

Albers, D., and Thaddea, S.: Electrocardiographic Changes in Experimental and Clinical Adrenal Insufficiency. *Ztschr. f. Kreislaufforsch.* 29: 825, 1937.

Adrenal insufficiency causes decreased amplitude of deflections, depression of S-T, and inversion of T. The deviations tend to return toward normal when the cortical hormone is supplied. The damage to the heart muscle was demonstrated histologically, but not in all cases.

KATZ.

Bellet, Samuel, and McMillan, Thomas M.: Electrocardiographic Patterns in Acute Pericarditis: Evolution, Causes and Diagnostic Significance of Patterns in Limb and Chest Leads; A Study of Fifty-Seven Cases. *Arch. Int. Med.* 61: 381, 1938.

The electrocardiographic findings in fifty-seven cases of acute pericarditis of different etiologic types are presented and discussed.

On the basis of these observations it is concluded that in a large majority of cases (80 per cent in this series) electrocardiographic changes are associated with pericarditis. In twenty-one cases (more than 37 per cent) the alteration in the RST segment conformed to a pattern which we regard as fairly characteristic, namely, elevation of the RST segment in the three limb leads, depression of the interval in Leads IV and V and elevation of the interval in Lead VI, with preservation of the initial downward deflection. In the remainder the inversion of the T-wave and minor changes in the RST segment, which are considered important, were noted. In the main, the deviation in the RST segment was observed in association with the more virulent forms of pericarditis, *e. g.* pneumococcal, uremic, and rheumatic; the alteration in the T-wave was the outstanding change present in cases of tuberculous pericarditis.

The deviation in the RST segment and the change in the T-wave are transient; for this reason it is important to obtain electrocardiographic records at frequent intervals.

The use of precordial leads as an important aid in the diagnosis is herein recorded; additional information was sometimes obtained by placing the anterior electrode over the area of friction.

The basing of a differential diagnosis on the electrocardiographic findings in cases of pericarditis and coronary occlusion is discussed.

Histologic studies of the cardiac muscle were made in nineteen of the cases of our series. From these observations, together with other factors mentioned, it is concluded that invasion of the subpericardial portion of the myocardium by pericarditis is chiefly responsible for the deviation observed in the RST segment.

Frequently, in spite of the presence of frank pericarditis, no electrocardiographic changes are observed. This is probably due to the absence of myocardial involvement or to the presence of an extremely slight grade of involvement.

AUTHOR.

Weicker, B., and Kessler, M.: Malaria and the Electrocardiogram. *Ztschr. f. Kreislaufforsch.* 30: 9, 1938.

Curves were taken on 25 patients with neurosyphilis during malarial therapy. In several instances changes were found indicative of coronary insufficiency. The majority, however, showed only minor changes. During treatment, the electrocardiogram may be a valuable adjunct in bringing to light latent myocardial damage in these patients.

KATZ.

Travell, Janet, Gold, Harry, and Modell, Walter: Effect of Experimental Cardiac Infarction on Response to Digitalis. *Arch. Int. Med.* 61: 184, 1938.

In the present study of fifty cats the effect of digitalis on the control animal is compared with that on the animal three weeks after experimental ligation of a coronary vessel with respect to the following points: the fatal dose, the dose necessary to produce a ventricular ectopic rhythm, the effect on the blood pressure, the changes in the R-T segment of the electrocardiogram, and the degree of healing of the infarct.

Previous studies have shown that within the first twenty-four hours after the experimental production of cardiac infarction the tolerance to digitalis is the same as that of the normal animal (cat and dog). In the presence of a partially healed infarct the cat (as well as the dog) is more susceptible to digitalis than the normal animal, requiring only about three-fourths as much digitalis as the normal animal to cause (a) a ventricular ectopic rhythm and (b) death. The larger the infarct, the more susceptible the animal; but many exceptions to this rule were observed, and some of the most susceptible animals had the smallest infarcts.

Treatment with aminophylline appeared to exert no effect on the tolerance to digitalis in cardiac infarction.

There is some indication that digitalis may cause displacement of the R-T segment in the electrocardiogram more readily in animals with cardiac infarction than in the normal animal.

Differences in tolerance may involve equally the fatal dose and that required to cause a ventricular ectopic rhythm, but the range of change tends to be greater for the former than for the latter. This appears to be true of differences in tolerance among apparently normal animals, as well as among those with cardiac infarction.

The facts indicate that increased susceptibility to digitalis in cardiac infarction may be due to a change in the properties not of the whole heart but of an area with impaired circulation within the zone of the infarct, from which abnormal impulses arise as the result of the administration of digitalis and precipitate ventricular tachycardia and fibrillation.

AUTHOR.

Binger, M. W., and Craig, W. McK.: *Atypical Case of Hypertension With a Tumor of the Adrenal Gland.* Proc. Staff Meet. Mayo Clin. 13: 17, 1938.

A case of essential hypertension is reported in which an adrenal tumor was found at the time of surgery carried out for relief of the hypertension by a resection of the splanchnic nerves. The patient seemed to have a typical case of essential hypertension. However, she had an extreme intolerance to heat and a basal metabolic rate of +61 per cent which could not be explained, as there was no evidence of hyperthyroidism. Following the first-stage operation for splanchnic resection, there was nothing unusual about the postoperative course. However, following the second stage of the operation performed twelve days after the first operation, the blood pressure rose to a very high level and remained so for a period of ten days. It was postulated that this unusual course of events might be due to some change in the right adrenal gland, and the patient was returned to the operating room and the old incision reopened. Immediately above the kidney a large tumor, measuring 6 by 3.5 cm., was found which proved microscopically to be a sympathicoblastoma. Following the removal of this tumor, the blood pressure returned to a low level, and it remained low up to the time of her dismissal. It was thought that the tumor had been activated by the manipulation incidental to the operation and that this was the cause of the excessive blood pressure reaction following the operation, although not necessarily the cause of the persistent hypertension which had been present previous to the operation.

HINES.

Burwell, C. Sidney: *A Comparison of the Pressures in Arm Veins and Femoral Veins With Special Reference to Changes During Pregnancy.* Ann. Int Med. 11: 1305, 1938.

The arm and leg venous pressures were studied in a group of nonpregnant persons including normal persons and those with conditions already known to affect local or general pressure and in a group of pregnant women and pregnant dogs. The direct method of measuring venous pressure described by Moritz and von Tabora was used in this study. The test was performed with the patient in the supine position in bed and with the zero of the manometer set at a level 5 cm. dorsal to the fifth dorsal cartilage. In individuals without heart disease or local obstruction, the venous pressure is nearly identical in the arm and leg under the conditions of this experiment. In the patients with congestive heart failure, the pressures are almost identical in arm and leg unless there is considerable ascites, in which case the leg pressure may be higher than the arm pressure. In pregnant women by the fourth month of pregnancy an increase takes place in the venous pressure in the leg which persists and even may increase throughout pregnancy. It was concluded that this increase was not due to increase in intraabdominal pressure but due to the pressure of the gravid uterus because when a pregnant dog's abdomen was opened the femoral venous pressure did not change. From these studies, it was concluded that venous collaterals developed when there is a higher degree of venous pressure in one area of periphery than in another. The higher pressures which were found in the femoral veins of pregnant women is thought to be due to the inflow of a large amount of blood through the placenta and obstruction of the outflow by the gravid uterus. A comparison of venous pressure in the different parts of the body may be helpful in the understanding and description of disease and may on occasion even be applied to diagnosis.

HINES.

Herrell, W. E.: Idiosyncrasy to Tobacco: Report of Case. *Proc. Staff Meet., Mayo Clin.* 13: 1, 1938.

A case is reported of a patient with hypertension in whom the smoking of tobacco produced marked elevation of the blood pressure. A rise in blood pressure as high as 60 mm. of mercury systolic and 50 mm. of mercury diastolic would occur after smoking one or two cigarettes. With abstinence from smoking, the blood pressure which had previously been elevated remained at a normal level, and his symptoms were much improved. The rise in the blood pressure after smoking a cigarette was almost identical with the rise produced by the cold pressor test. It was assumed that this patient would give an exaggerated vasoconstrictor response to many different stimuli and that tobacco particularly would produce a marked vasoconstrictor response with a resulting marked elevation of the blood pressure. Further studies regarding the effect of tobacco on the blood pressure should be carried out. It seems to be wise to advise patients who have hypertension to smoke lightly or not at all if tests show that their blood pressure is influenced by the use of tobacco.

HINES.

Goodman, Charles: Thrombo-Angiitis Obliterans and Typhus (Evidence of Etiologic Relationship). *Arch. Surg.* 35: 1126, 1937.

Success in the treatment of disease, with few exceptions, has not been obtained until the causative factor has been described. In this respect, thromboangiitis obliterans is typical. Many etiologic agents have been considered as the cause of thromboangiitis obliterans, but in no case has there been definite proof that the suspected agent was the real cause of the disease. An etiologic relationship between typhus fever and thromboangiitis obliterans has been suspected for many years. A cutaneous test has been devised which gives a positive reaction over a long period of time in patients who have had typhus. This test is uniformly negative in normal persons and in a group of patients with arteriosclerosis and diabetes. It is almost uniformly positive in a group of 94 adults with thromboangiitis obliterans. These findings are highly suggestive of an etiologic relationship between typhus and thromboangiitis and open the way for further research along this line.

HINES.

Tartakoff, Joseph, and Hazard, J. Beach: Thromboangiitis Obliterans of the Spermatic Cord. *New England J. Med.* 218: 173, 1938.

A Russian Jew, aged 28 years, presented symptoms of a dragging sensation in the left groin and the left half of the scrotum, of less than four weeks' duration. There were no other symptoms, and no evidence by physical examination of vascular disease in the extremities. There was moderate tenderness of the left spermatic cord, and a palpable mass the size of a cherry in the cord about 1 cm. above the epididymis. The mass was removed surgically. Microscopic examination revealed changes characteristic of thromboangiitis obliterans, with no tubercle-like lesions. The veins, 0.3 to 1.3 mm. in diameter, were occluded by partly organized and partly canalized thrombi. The smaller vessels, including the arterioles, presented patent lumens and normal lining surfaces and vessel walls. Cellular changes consistent with the diagnosis of thromboangiitis obliterans were found. A diagnosis of nonspecific thrombosis of the spermatic venous plexus was considered untenable because a more extensive lesion would be expected than the one found.

MONTGOMERY.

Anthony, A. J., and Loos, W.: The Distensibility of the Blood Vessels of the Human Extremities. I. *Ztschr. f. Kreislaufforsch.* 30: 1, 1938.

The authors determined the pulse wave velocity of the blood vessels of extremities in normal persons at various internal pressures. They used a large pressure cuff to decrease the effective internal pressure in the vessels. This led regularly to a decrease in pulse wave velocity. The correlation curve between pulse wave velocity and internal arterial pressure characterizes the properties of the vessel wall.

KATZ.

Lent, W.: The Distensibility of Vessels of the Human Extremities. II. *Ztschr. f. Kreislaufforsch.* 30: 55, 1938.

When pulse wave velocity is correlated with systolic pressure, the curve is found to be shifted to the right in hypertensive and elderly patients, as compared with the normal; but when the correlation is made with diastolic pressure, no difference in the curves of the abnormals and normals is found.

It is shown that the pulse pressure can be computed from the curve relating pulse wave velocity to the systolic pressure.

KATZ.

Kountz, William B., and Smith, John B.: The Flow of Blood in the Coronary Artery in Pathological Hearts. *J. Clin. Investigation* 17: 147, 1938.

In hearts of patients who have died of heart failure, the coronary blood flow is diminished either absolutely, as in diseases of the coronary arteries and in dilatation of the heart, or relatively, as in hypertrophy.

Under the conditions of these experiments, it appears that any rate of flow less than 0.75 per gram of heart muscle per minute endangers the function of the heart.

Either hypertrophy or dilatation reduces the coronary flow per gram of heart muscle. In hypertrophy this may be accounted for by increase in muscle mass. In dilatation, lengthening and stretching of coronary vessels may be the chief factor.

In dilated hearts the coronary flow is increased during systole and diminished during diastole; a result which is exactly opposite to that found in hearts of normal diastolic volume.

In the dilated heart drugs which tend to decrease the diastolic volume increase the coronary flow, while those which augment diastolic volume diminish the flow. This action also is directly opposite to the phenomena observed in normal, undilated hearts. It suggests that the physical state of the heart, and particularly the degree of dilatation, must be considered in the selection of drugs for the treatment of cardiac disease.

AUTHOR.

Aschoff, L.: Normal and Pathologic Anatomy of Senility. 3. The Circulatory System in Senility. *Med. Klin.* 33: 353, 1937.

The following changes in senility were observed: (1) decreased heart weight (but in the presence of atherosclerosis and hypertension cardiac hypertrophy was found), (2) valve deformities on the left side, and (3) fatty infiltration of the pericardium. The capillaries were practically unchanged in number.

KATZ.

Albers, D.: Viscosity of Blood in Cardiac Insufficiency. *Ztschr. f. Kreislaufforsch.* 29: 915, 1937.

Blood viscosity is increased in heart failure. This occurs also in the presence of anemia when the effect of the anemia itself on the viscosity is discounted. The only exception is in thyrotoxicosis. As the patient improves, viscosity goes back toward normal. There is no parallelism between viscosity and blood pressure. Diuretics and venesection and raw food lower blood viscosity.

KATZ.

Kramer, David W.: Periodic or Intermittent Venous Compression in the Treatment of Peripheral Vascular Disease. *M. Rec.* 147: 99, 1938.

The method is that recently revived by W. S. Collens and N. D. Wilensky. It consists of intermittent, automatic compression of a thigh at a pressure of 30 to 80. mm. Hg.

Thirty patients with peripheral vascular disease were treated for a total of four hundred hours. Twelve had diabetes; seven, Buerger's disease; five, arteriosclerosis; and four, phlebitis.

Twenty of the patients were benefited; five were slightly or temporarily improved; five were not benefited. Cramps and fatigue were relieved; pain did not respond so satisfactorily. An occasional skin temperature reading showed a rise in skin surface temperature averaging 1 to 3° C. in most of the patients tested. An increase in oscillographic readings was noticed immediately after the treatment, and at the termination of treatments, in those tested. The author thinks that intermittent venous occlusion is a desirable addition to the more recent methods of treatment of vascular diseases but considers the negative and positive pressure apparatus as the outstanding contribution.

MONTGOMERY.

Gold, Harry, Otto, Harold, Kwit, Nathaniel T., and Satchwell, Harry: Does Digitalis Influence the Course of Cardiac Pain? A Study of 120 Selected Cases of Angina Pectoris. *J. A. M. A.* 110: 859, 1938.

The effect of digitalis medication on cardiac pain was investigated in a series of 120 patients with angina pectoris.

The following criteria were used for the selection of these patients: evidence of organic heart disease, absence of signs of congestion, cardiac pain on effort, doing little or no physical work, and faithful cooperation.

The effect studied was the influence on the severity and frequency of attacks of pain and on the capacity for effort without pain. The data were secured in accordance with a plan designed to reduce to a minimum common sources of error and in a manner relatively free from bias by the use of the "blind test."

In all, 243 courses of treatment with fairly large daily doses of digitalis (from 0.2 to 0.6 gm.) were given, each lasting an average of eleven weeks and being alternated with a course of a placebo of lactose or some other agent.

The course of the pain was charted, the habitual status as well as graded departures from it being represented in every case. The causal relation was established by a method relatively free from personal judgments; namely, by comparing sections of the chart representing, respectively, placebo and digitalis periods.

The results show that nearly one-half of all the patients reported a departure from their habitual status on their return visit after the first course of treatment

with digitalis; in about 15 per cent the pain was increased and in about 30 per cent it was diminished. Results bearing a strong similarity to these were obtained, however, during the use of a placebo.

In most cases the change in pain failed to persist when administration of the drug was continued or failed to reappear during repeated courses of digitalis.

In the remaining cases in which the change recurred when the course of digitalis was repeated, it was possible to digitalize fully without any apparent effect on pain by altering the form, color, or flavor of the preparation of digitalis.

It is concluded from these facts that in cases of angina pectoris without congestion the likelihood is negligible that the use of digitalis will, by a direct action on the circulation, increase or diminish cardiac pain.

In view of the fact that the patients of this series were presumably unusually susceptible to cardiac ischemia, the results indicate further that digitalis even in large doses rarely, if ever, produces effective constriction of the coronary arteries in man.

AUTHOR.

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